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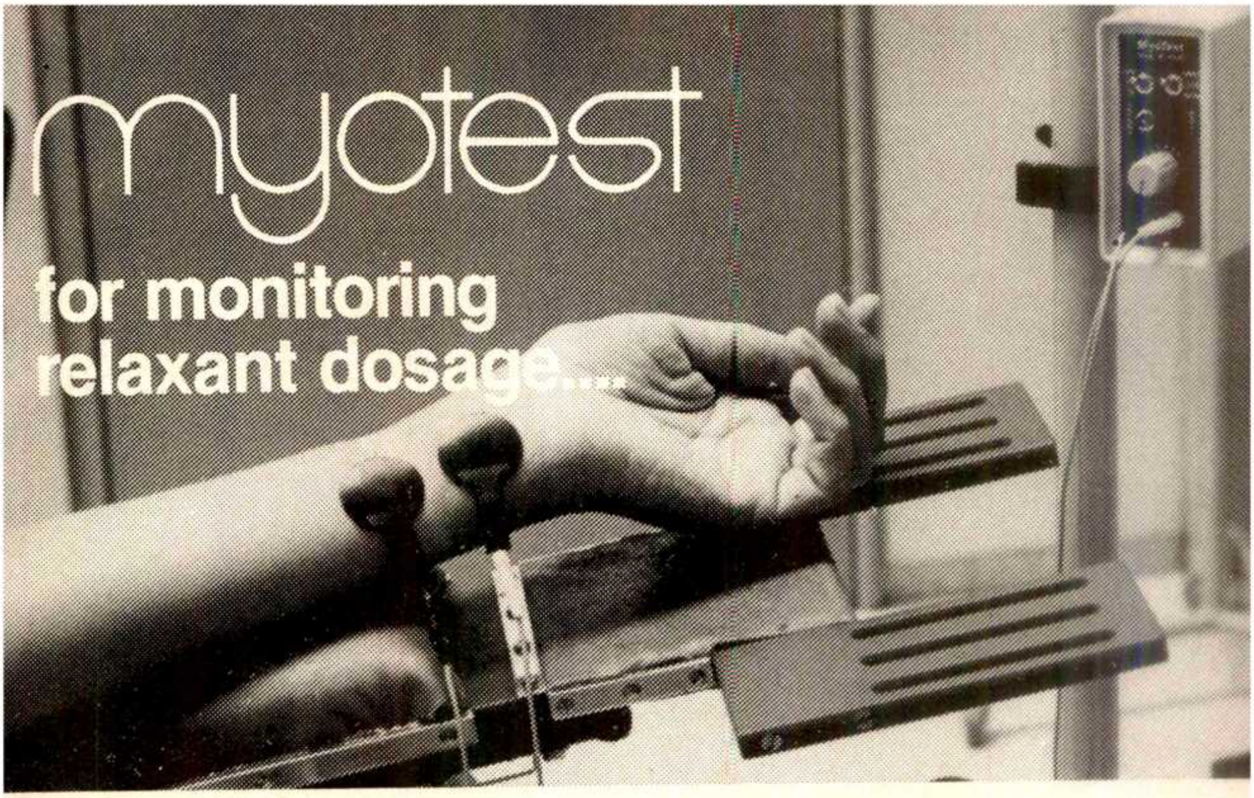

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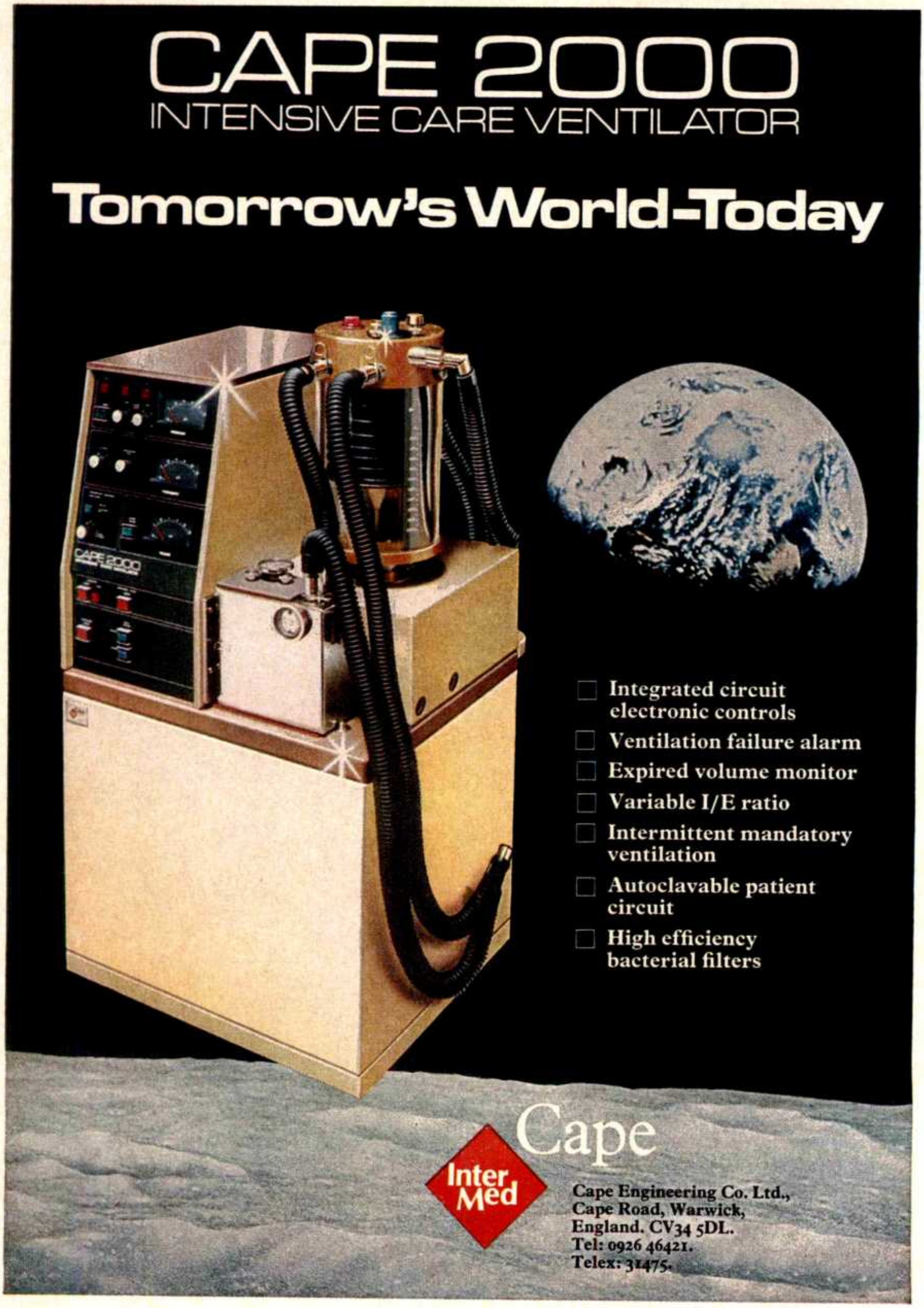

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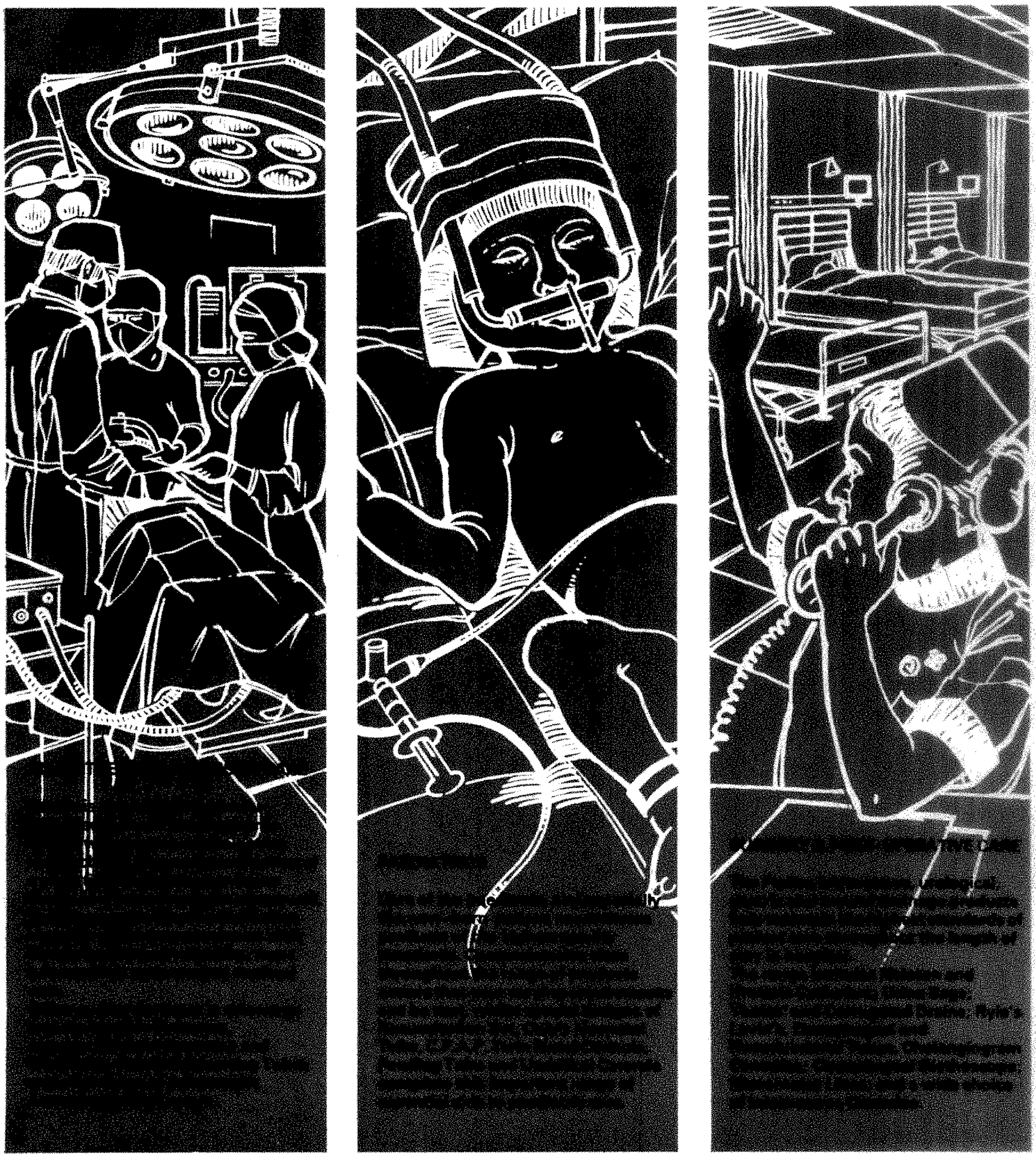

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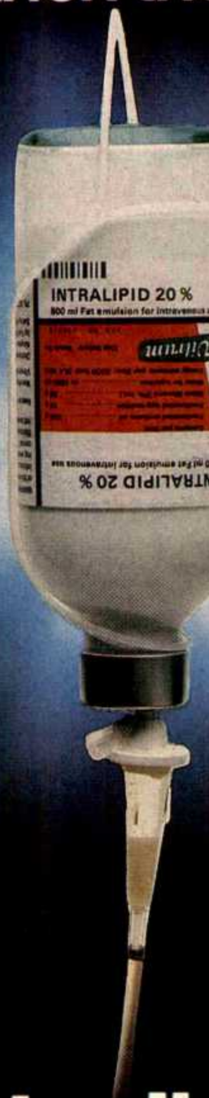

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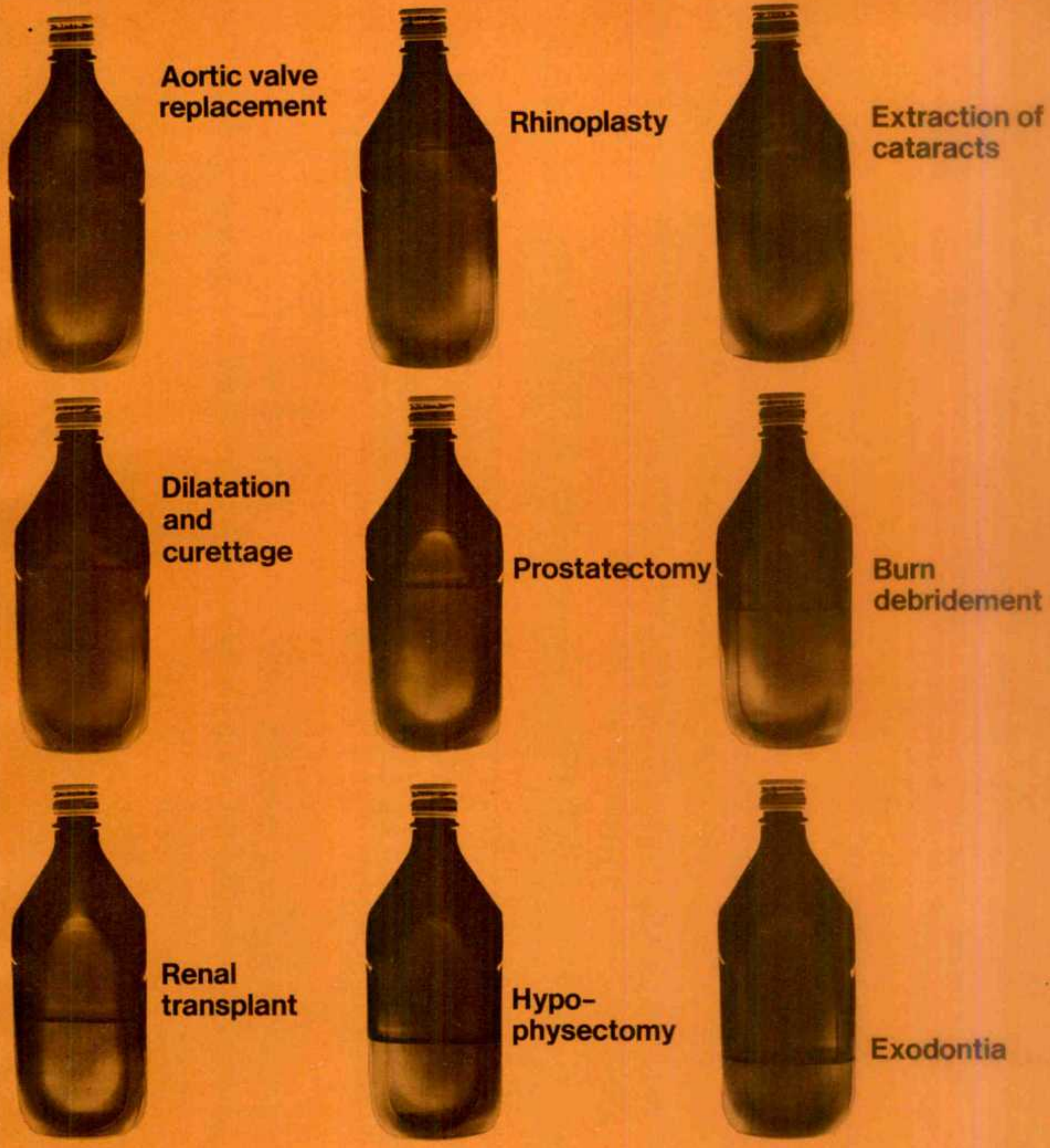

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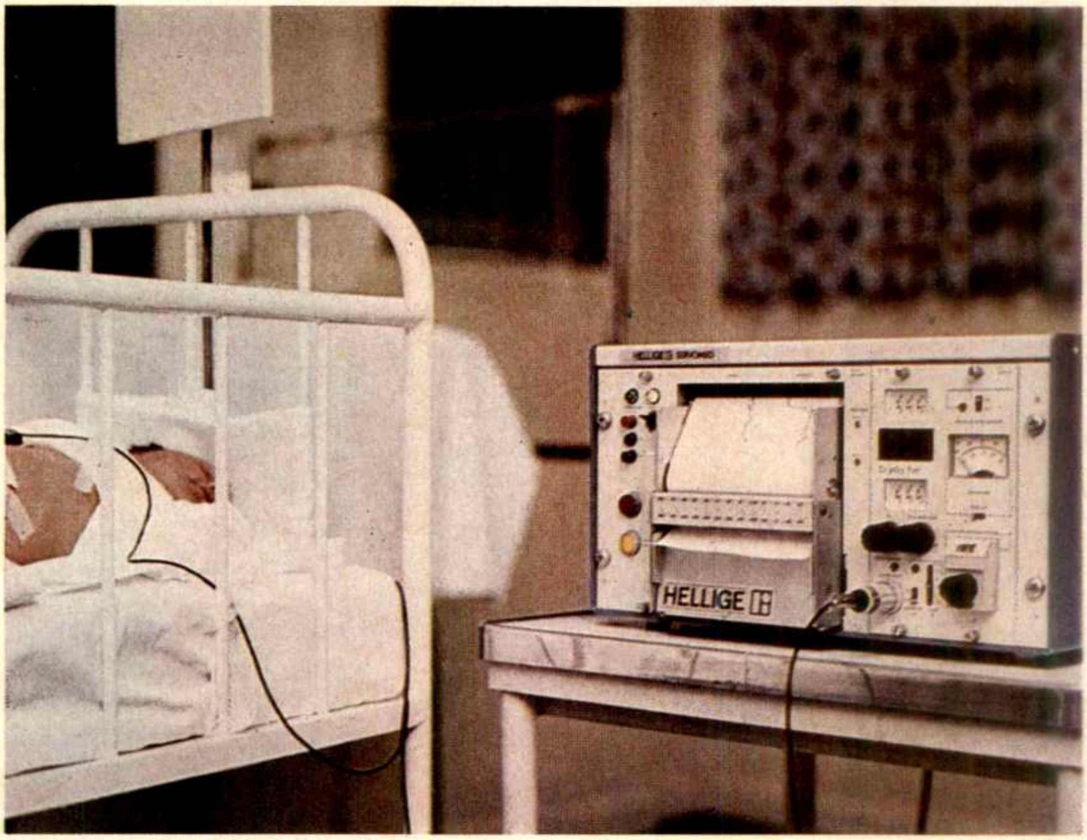

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1) Schneider et al., Chirurg **47,** 185 (1976)
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VOLUME 51, No. 7 JULY 1979

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EDITORIAL

ANAESTHETIC PHARMACOLOGY

The practice of clinical anaesthesia depends on a thorough understanding of the pharmacology of the drugs used. Cynics might suggest that there have been few significant advances in the past 25 years. For example, thiopentone remains the most popular i.v. induction agent and morphine is the most widely applicable potent analgesic. Not that these drugs are trouble-free, but we are accustomed to their side-effects and dangers. The difficulties found with new drugs are often not that they are more toxic, but that they produce different problems. Nephrotoxicity was unexpected when methoxyflurane was introduced, as were the hypersensitivity reactions seen with propanidid. Advances are occurring, however, and each new drug is being evaluated much more critically in assessing its value and limitations.

This issue of the Journal is devoted to reviewing some aspects of general pharmacology and some of the types of drugs that anaesthetists encounter. Increasingly it is now possible to measure the concentration of drugs and their metabolites in the body and to determine where they are acting. Some of the various models available to describe the distribution, elimination and action of drugs are reviewed. These may help in the designing of better ways of administering drugs to ensure that the correct concentrations are achieved at the receptors for a sufficient time. Whilst volatile anaesthetics are used to maintain anaesthesia at a reasonable constant blood concentration, it does seem strange that we use many of our other drugs as repeated i.v. boluses with fluctuating blood concentrations. The awakening of interest in total i.v. anaesthetic regimes shows that other administration techniques are feasible.

The ways in which new drugs are introduced and accepted or rejected would form a good subject for study. Over-optimistic fanfares such as that accompanying the introduction of ketamine into the United Kingdom do not help. Ketamine has a small and useful role, perhaps mainly outside the operating theatres. The introduction of other drugs such as fazadinium and etomidate has been more gradual and both are now available, but some of the initial reports commented on adverse features, whilst others praised the drugs. Probably only their general release will determine whether their advantages outweigh their disadvantages. It may surprise some of our American readers that enflurane is only now reaching the United Kingdom market. We can gain from the extensive experience of it across the Atlantic and it seems destined to replace methoxyflurane and compete strongly with halothane. It is welcome that it is being delivered only from calibrated vaporizers. Surely the time has passed when unknown concentrations of potent inhalation agents are administered to patients. Delays in introducing drugs found useful in Europe into the United States are not unknown. Perhaps the various national agencies responsible should get together to set international standards.

The pharmacology of anaesthesia is developing rapidly and anaesthetics must be capable of placing new knowledge of the actions of drugs in the context of normal physiology, the effects of pathological conditions such as renal and hepatic failure and the possible interactions that may occur between drugs. Polypharmacy is increasing: so are the possibilities of unusual effects.

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(*Br. J. Anaesth.*, **51**, 339)

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Br. J. Anaesth. (1979), **51**, 579

PHARMACOKINETICS AND PHARMACODYNAMICS

C. J. HULL

The science of *pharmacokinetics* has evolved from the quantitative study of drug concentrations in the tissues of the body, while *pharmacodynamics* considers the relationships between drug concentration and pharmacological effect.

Pharmacokinetics is considered by many clinicians to be an esoteric mathematical game having little or nothing to do with clinical pharmacology; in truth it is the means by which we are slowly coming to understand and in some cases predict the dose–response relationships of commonly used drugs.

When a drug is administered to a patient, the onset and duration of its effect depend upon the rate of absorption into the bloodstream, distribution to various organs, tissue binding, access to those tissues where the pharmacological effect takes place, interaction with receptor sites, and elimination by various routes (fig. 1). Since the body is composed of innumerable tissue zones, each with a unique blend of perfusion, solubility, binding affinity, etc., for the drug, quantification of the whole process would seem impossible unless some gross simplifications can be made.

From the point of view of a particular drug, the body can be thought of as comprising one or more *compartments*, each of which can be considered to be a space throughout which the substance is uniformly distributed, and has uniform kinetics of distribution or transport (Sheppard, 1948).

The one-compartment model

Some drugs behave as if they were distributed into a single uniform compartment, from which excretion takes place in a "first-order" manner. (This simply means that in each time period, a constant proportion of the remaining drug will be eliminated; that is, the elimination rate is proportional to the concentration.)

When the drug concentration decreases in this "constant proportion" manner, the concentration curve (fig. 2) can be defined by a simple exponential equation:

$$C/C^0 = e^{-kt} \qquad (1)$$

where

C = drug concentration at time t

C^0 = drug concentration at time 0 (i.e. immediately after i.v. administration)

k = a constant

t = elapsed time in hours

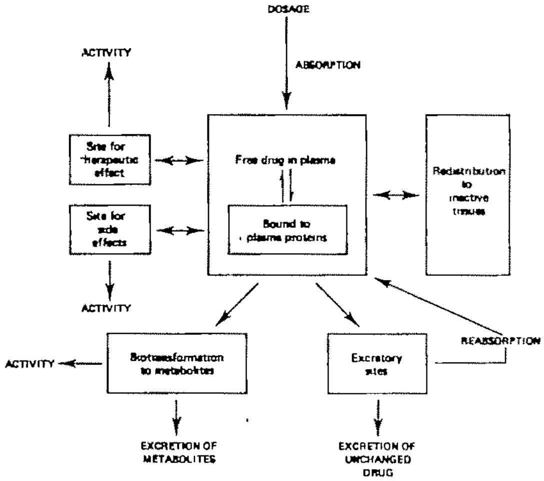

FIG. 1. Some of the possible pathways for the uptake, distribution and elimination of an active drug.

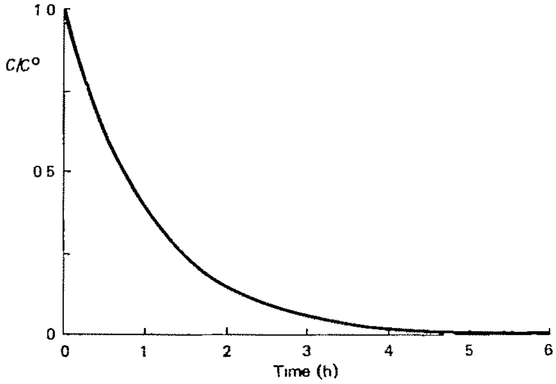

FIG. 2. Exponential decline of drug concentration in a one-compartment system. (C^0 = drug concentration when t = 0.)

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e = 2.718, the base of the natural logarithm*

If we take the natural logarithm of both sides of equation (1), a linear equation is developed:

$$\ln (C/C^0) = -kt \qquad (2)$$

so that after rearrangement

$$\ln(C/C^0)/t = -k \qquad (3)$$

Thus the natural logarithm of the *proportion* by which C has decreased to *time* is a constant (k). This constant has the dimension of *rate*, and will in this case be quantified in units of reciprocal hours (h^{-1}). It further follows that a graph of $\ln(C/C^0)$ against time should yield a straight line, of gradient $-k$ (fig. 3). The dimension of the first-order rate constant k should now be clear, as it is the number of "log units" by which the concentration decays *per hour*. (If we had used ordinary logarithms, a plot of $\log (C/C^0)$ against time would have yielded a straight line, but the gradient would not be $-k$ but $-k/2.303$. The convenience of the natural logarithm should now be clear.)

Two other parameters are at times useful.

The *time constant* (τ) is simply the reciprocal of the rate constant, so that

$$\tau = 1/k \qquad (4)$$

and therefore

$$C = C^0 . e^{-t/\tau} \qquad (5)$$

τ is the time at which C *would* decrease to zero if it continued to decline at its initial rate. During 1 time constant, drug concentration decreases to $0.37C^0$ (37% of the initial concentration) (i.e. a 63% decrease from the initial concentration) (fig. 4). After 2 time constants C decays to $0.14C^0$, and after 4τ, to $0.02C^0$.

The time constant is useful in that it emphasizes the *constant proportion* nature of the decay.

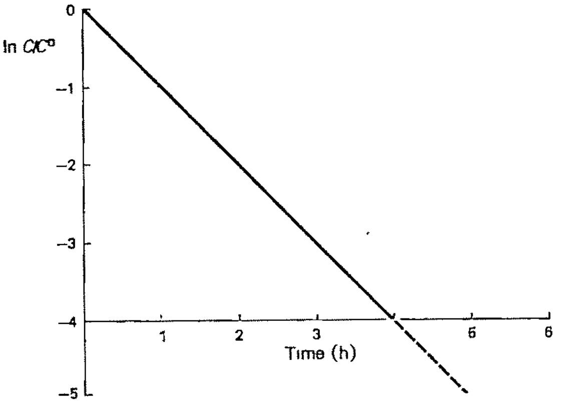


FIG. 3. Figure 2 replotted on semi-logarithmic ordinates shows the linear relationship between $\ln (C/C^0)$ and time.

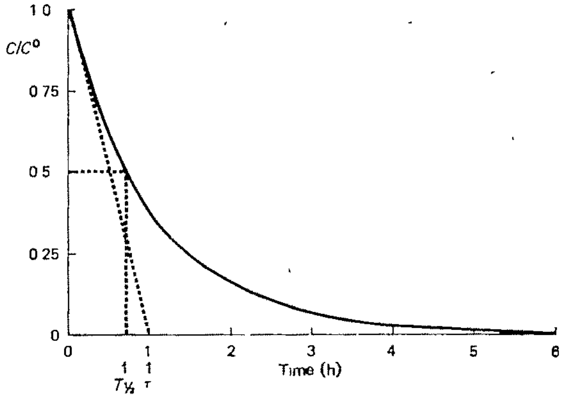


FIG. 4. The relationship between time-constant (τ) and half-life ($T_{\frac{1}{2}}$) in an exponential decay. If $\tau = 1$ h, then $T_{\frac{1}{2}} = 0.693$ h.

The *elimination half-life* ($T_{\frac{1}{2}}$) is the period after which C has decreased to exactly $0.5C^0$, and is easily derived from a simple rearrangement of equation (2):

$$t = \ln(C/C^0)/-k \qquad (6)$$

Since we wish to solve for $C/C^0 = 0.5$, and $\ln 0.5 = -0.693$, it follows that

$$T_{\frac{1}{2}} = 0.693/k \qquad (7)$$

or

$$T_{\frac{1}{2}} = 0.693\tau \qquad (8)$$

To show that such convenient characteristics do in fact occur in nature, let us examine the serial plasma concentrations of bromsulphthalein (BSP) after a single i.v. injection (fig. 5, based on data from Wichmann, Rind and Gladtke, 1968).

It is apparent that in this plot of $\ln C$ against time, the plasma log concentrations *do* decay in a straight line, thus satisfying the conditions for a one-compartment, first-order model. (BSP is highly

---

* The logarithm of a number is the *power* to which a *base* must be raised to yield that number. In ordinary logarithms the base is 10; in natural logarithms it is 2.718 . . . (rounded to 3 decimal places). Thus the ordinary and natural logarithms of 10 and 100 can be expressed:

$$\log 10 = 1; \ln 10 \simeq 2.303$$
$$\log 100 = 2; \ln 100 \simeq 4.605$$

Note that in each case, the natural logarithm is 2.303 times greater than the ordinary. The anti-logarithmic process is just as simple, except that in natural logarithms the more explicit symbols e^x or exp are used. (The anti-logarithm is of course the base raised to the power of the logarithm (x).) Thus $e^{2.303} \simeq 10$ and $e^{4.605} \simeq 100$.

Using the exp notation:

$$\exp 2.303 \simeq 10 \quad \text{and} \quad \exp 4.605 \simeq 100.$$

This paper uses *natural* logarithms throughout with ln and e^x denoting logarithm and anti-logarithm.

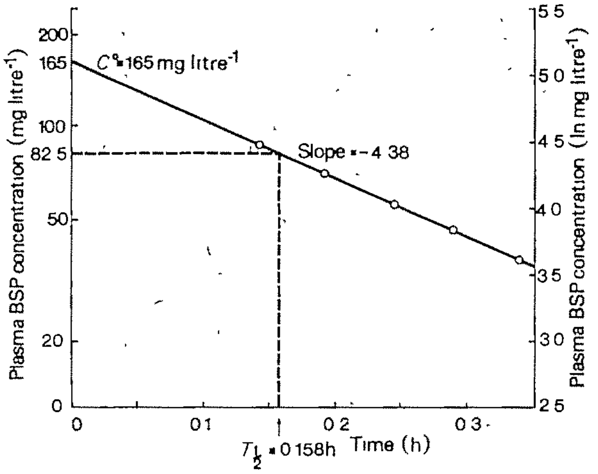


FIG. 5. Plasma concentrations of BSP following a 20-mg i.v. dose, plotted on semi-logarithmic ordinates. Since C^0 = 165 mg litre^{-1}, $T_{\frac{1}{2}}$ is the time taken to decline to 165 × 0.5 = 82.5 mg litre^{-1} (i.e. 0.158 h).

bound to plasma proteins so that only an insignificant proportion leaves the circulation.)

If the straight line in figure 5 is extrapolated back to $t = 0$, the half-life ($T_{\frac{1}{2}}$) is seen to be approx. 0.158 h, so that by solution of equation (7), the rate constant k is 0.693/0.1582 = 4.38 h^{-1}, and the time constant τ = 0.23 h. From the value of $\ln C$ at $t = 0$ (C^0) it can now be estimated that the i.v. injected dose (Xd) produced an initial concentration C^0 of 165 mg litre^{-1}. If we assume that the 20 mg of BSP is uniformly distributed, then the compartment must have a volume of distribution of 20/165 = 0.121 litre, that is,

$$V = Xd/C^0 \tag{9}$$

It must be appreciated that this is an *imaginary* volume, since it is presumed to exist purely by virtue of the measured dilution of the injected dose. (It is perfectly possible for a drug to have a distribution volume of >300 litre, as is indeed the case for pethidine (Klotz et al., 1974).) The model is conventionally characterized by the diagram of figure 6.

It will be clear that while k defines the rate of decline of drug *concentration*, it tells us nothing of the actual process of elimination. This process, or *clearance*, can be defined as the *rate of drug removal* (g h^{-1}) *per unit of drug concentration remaining in the model* (g litre^{-1}). Clearance (Cl) thus has the dimension: gram/hour × litre/gram, which simplifies to litre/hour, or litre h^{-1}. It can be readily calculated as the product of *volume* (litre) and *rate constant* (h^{-1}). Thus:

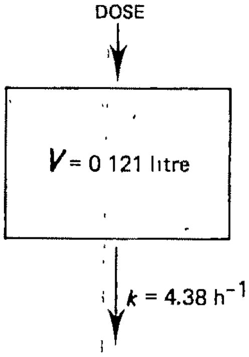


FIG. 6. A one-compartment open model for BSP, derived from the data of figure 5.

$$Cl = V.k \text{ litre h}^{-1} \tag{10}$$

(Clearance can also be estimated by dividing the dose by the area under the concentration curve from the time of administration (t^0) to infinity (t^∞).

Having the dimension of flow, clearance is often referred to as the volume of compartment *completely cleared* of drug per hour. In compartmental kinetics, this concept, although valid, is not especially helpful, since it is not descriptive of what actually happens. (Those readers with an understanding of simple electronics will recognize that a one-compartment open model can be compared with a *capacitor* discharging through a *resistor* (see Hull and McLeod, 1976). In terms of this simple electrical analogue, *clearance* can be identified with the reciprocal of the resistance, i.e. the *conductance* of the resistor.)

Taking the BSP example, we can calculate clearance by solving equation (10), so that Cl = 0.121 × 4.38 = 0.53 litre h^{-1}.

Thus BSP is removed as if 0.53 litre per hour were completely cleared of drug. It is more useful to restate the result as:

> "For every g litre^{-1} concentration in the model, the excretion mechanism will remove 0.53 g h^{-1} of BSP."

In practice, very few drugs behave according to one-compartment kinetics, since some initial redistribution from the circulation to other tissues is almost inevitable.

The two-compartment model

Frequently, the serial plasma concentrations after an i.v. dose of drug show an initial rapid decay, followed by a linear decline when plotted on the same semi-logarithmic axes as before. Figure 7 shows as an illustrative example, the decay of plasma pancuronium concentration after a 4-mg i.v. injection (Hull and McLeod, 1976). The curve of best fit is a bi-exponential decay, which is characteristic of drug concentration in the central compartment of a two-compartment "open" model, in which drug is assumed to enter a "central" compartment (V_1), from which it is also eliminated. Drug is also redistributed to a "peripheral" compartment (V_2), from which elimination does *not* take place except by transfer to the central compartment.

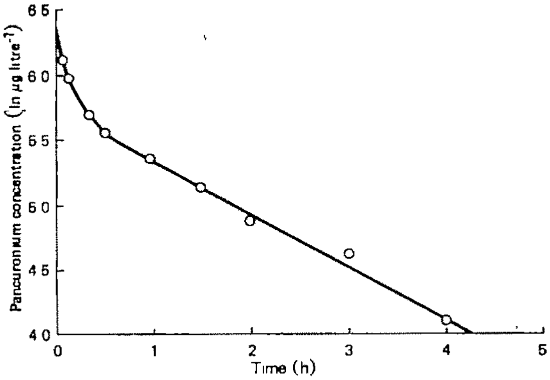


FIG. 7. Plasma pancuronium concentrations after a 4-mg i.v. dose, plotted on semi-logarithmic ordinates. The solid line is the best fitting bi-exponential curve. (From Hull and McLeod, 1976.)

The initial rapid decay (α phase) is mainly the result of the redistribution of drug from compartment one to compartment two, and the slower terminal decay (β phase) is principally associated with drug elimination.

The equation describing the time course for C_1 (the concentration in the first compartment) is more complex than that for the one-compartment system:

$$C_1 = A . e^{-\alpha t} + B . e^{-\beta t} \qquad (11)$$

A, B, α and β are constants, which are best understood by referring to figure 8. The solid bi-exponential curve is the sum of the two single exponentials (dotted), A declining at rate α, and B declining at rate β.

Thus

$$C^0 = A + B \qquad (12)$$

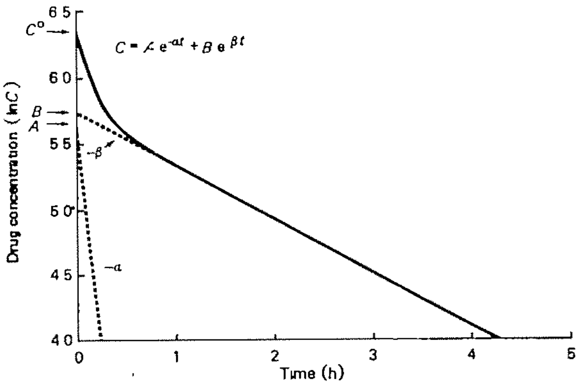


FIG. 8. The characteristics of bi-exponential decay. The (solid) bi-exponential curve is the sum of the two single exponential (dotted) lines. The initial concentration (C^0) is the sum $A+B$. Semi-logarithmic ordinates.

In the simple one-compartment model, the exponent k (in equation (1)) *is* the elimination rate constant, but the two-compartment model is less straightforward: α and β are *hybrid* rate constants, since α does not exclusively relate to redistribution, nor β to elimination. The parameters of the compartmental model can, however, be derived from equation (11) by application of a sequence of formulae (Portman, 1970):

$$V_1 = \text{Dose}/(A+B) \qquad (13)$$

$$k_{21} = (A\beta + B\alpha)/(A+B) \qquad (14)$$

$$k_{10} = \alpha\beta/k_{21} \qquad (15)$$

$$k_{12} = \alpha + \beta - k_{21} - k_{10} \qquad (16)$$

$$V_2 = V_1 . (k_{12}/k_{21}) \qquad (17)$$

Figure 9 shows the two-compartment model derived from the pancuronium example. Fitting a bi-exponential function to a series of points has traditionally presented a thorny problem, but a number of computer programs have now been developed (e.g.

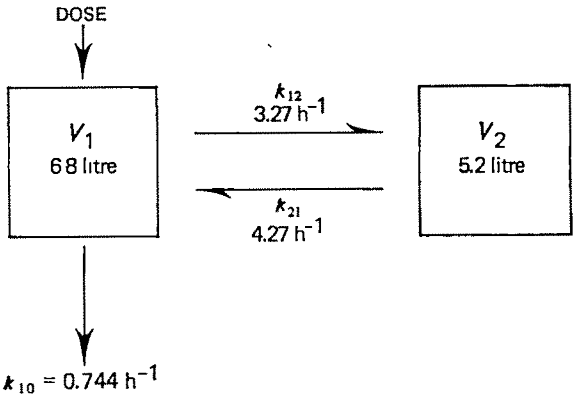


FIG. 9. A two-compartment model for pancuronium, derived from the bi-exponential decay in figure 7. k_{10} is the elimination rate constant.

Holland, 1976) to overcome this difficulty. The reader is referred to Riggs (1963) and Atkins (1969) for detailed analyses of the errors involved.

Drug is assumed to enter and leave the model only through compartment one. It is assumed that drug is both distributed and eliminated by first-order processes (i.e. the rate of drug transfer is proportional to the concentration difference). Since it is assumed (here) that drug behaves isotropically (i.e. moves equally easily in both directions), the rate of transfer will be the same in either direction for a given concentration gradient.

The actual rate of *concentration* decline will, then, depend upon the compartmental *volume* from which drug is being cleared. Since, in this case, V_1 and V_2 are different, k_{12} and k_{21} must also be different. The clearances ($V_1.k_{12}$, and $V_2.k_{21}$) are, of course, identical.

Figure 10 shows the changing drug concentrations in both compartments of the model following a single dose. The compartment one curve is, of course, that for plasma already shown in figure 7. That for compartment two is also a bi-exponential function:

$$C_2 = P.e^{-\alpha t}+Q.e^{-\beta t} \tag{18}$$

Note that the exponents, α, β are the same as those for C_1, but the constants P and Q are different. Q will in fact be similar to B (reflecting the similar terminal phases), but P is negative (and equals Q), yielding the positive initial slope from $C_2{}^0 = 0$ at $t = 0$. Initially the drug concentration in the second compartment increases. At the inflection of the C_1 curve, the two lines cross and the concentration gradient is reversed. Up to this point (α phase), drug moves from the first to the second compartment; thereafter it moves the other way. During the β phase, the log concentration difference between the two compartments remains constant, in keeping with their first-order relationship. Thus on a semi-logarithmic plot (fig. 10) the concentrations C_1 and C_2 decline in parallel, in a state of quasi-equilibrium. In a true equilibrium there would be no net movement of drug in either direction, since there would be identical concentrations in both compartments.

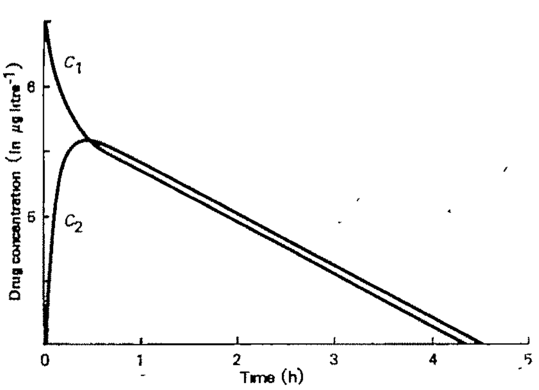


FIG. 10. Drug concentrations in both compartments of the two-compartment model of figure 9, following a 4-mg bolus of drug into the central compartment (V_1). Semi-logarithmic ordinates.

It has been shown that pancuronium is eliminated by the kidney and is also metabolized (Agoston et al., 1973) so that k_{10} has two components. So long as elimination takes place from the central compartment, k_{10} is simply the sum of the individual constants, so that, if renal elimination occurs at rate k_R and hepatic degradation at rate k_H:

$$k_{10} = k_R+k_H \tag{19}$$

Kinetic studies suggest that, in the case of pancuronium, elimination is probably equally shared by the two routes (McLeod, Watson and Rawlins, 1976; Somogyi, Shanks and Triggs, 1977).

The definition of "distribution volume" of the two-compartment model has been the subject of much discussion. It is very tempting to consider the decline in plasma concentration during the terminal, apparently mono-exponential phase, and to treat the system *as if it were* a single compartment system. The apparent distribution volume (V^β) can then be calculated from the expression:

$$V^\beta = (V_1.k_{10})/\beta \tag{20}$$

Calculated for the "pancuronium" example, $V^\beta =$ 12.55 litre. ($\beta = 0.403$ h^{-1}.)

V^β is in fact a proportionality constant which relates the amount of drug in the body to the plasma concentration at any time during the terminal phase (Gibaldi and Perrier, 1975). It is only an *approximate* index of distribution volume, as it is dependent upon k_{10}, and, in the case of rapidly eliminated drugs, will seriously overestimate the total distribution volume.

The correct distribution volume is simply the sum of V_1+V_2 (Riggs, 1963) and has been more formally defined as the steady-state distribution volume V^{ss} (Klotz, 1976).

Under steady-state conditions (i.e. after a long constant-rate infusion) the distribution volume can be defined as the mass of drug in the body (X^{ss}) divided by the concentration (C^{ss}). Since, at steady state both compartments have the same concentration, the *plasma* concentration can be taken as representing C^{ss}.

Thus

$$V^{ss} = X^{ss}/C^{ss} \tag{21}$$

Since it is possible to derive X^{ss} from the area under the plasma concentration–time curve as it increases from zero to C^{ss}, V^{ss} can be calculated (equation (21)) without reference to the compartmental model. For this reason, V^{ss} is often referred to as a model-independent parameter. It is important to appreciate that V^{ss} is only model-independent if calculated *by this method.* If taken to be $V_1 + V_2$ it is, of course, wholly dependent upon the choice of model.

In our pancuronium example, $V^{ss} = 12.0$ litre $(V_1 + V_2)$, so that V^{β} overestimated V^{ss} by 4.3%. If we had taken data for fazadinium, which appears to be more rapidly eliminated than pancuronium (Duvaldestin et al., 1978), the error would have been greater.

As in the one-compartment system, half-life ($T_{\frac{1}{2}}$) is a useful parameter, but is, at first sight, difficult to derive from a biexponential curve. If we consider equation (11), drug concentration can be seen to equate with the sum of two terms, $A.\mathrm{e}^{-\alpha t}$ and $B.\mathrm{e}^{-\beta t}$. Now, since coefficient α is much larger than β (i.e. slope α is steeper than β in fig. 8), $A.\mathrm{e}^{-\alpha t}$ will approach zero at a time when $B.\mathrm{e}^{-\beta t}$ still has a finite value, so that equation (11) can be reduced to

$$C_1 = B.\mathrm{e}^{-\beta t} \tag{22}$$

Equation (22) is, of course, a mono-exponential function, so that the half-life can be expressed (as in equation (7)) as

$$T_{\frac{1}{2}}{}^{\beta} = 0.693/\beta \tag{23}$$

$T_{\frac{1}{2}}{}^{\beta}$ is in this case usually referred to as the "elimination half-life", which makes clear the limitation of the parameter to the β (elimination) phase of the decay, but it must be appreciated that β depends upon both elimination *and* distribution rates, so that $T_{\frac{1}{2}}{}^{\beta}$ should not be regarded as a direct indicator of elimination rate. It is, however, extremely useful for determining the effects of *multiple* doses to the model. Drug elimination is better expressed by clearance as in the one-compartment system. Remembering that clearance Cl is the product $V.k$ (equation (10)), and that all drug leaves the two-compartment model via V_1, we can equate whole-model clearance with that of V_1:

$$Cl = V_1.k_{10} \tag{24}$$

Now if equation (20) is rearranged, we can obtain:

$$V^{\beta}.\beta = V_1.k_{10} \tag{25}$$

so that

$$Cl = V^{\beta}.\beta \tag{26}$$

This alternative derivation for clearance can in fact be a useful way of obtaining V^{β} if Cl has already been calculated by an "area under the curve" method. If equations (23) and (24) are applied to the pancuronium model, the elimination half-life ($T_{\frac{1}{2}}{}^{\beta}$) and clearance ($Cl$) are found to be 1.72 h and 5.06 litre h^{-1} respectively.

The three-compartment model

The plasma concentrations of some drugs do not decline in a conveniently bi-exponential fashion, but follow a smoother curve which is better fitted by a three-exponential equation of the form:

$$C_1 = A.\mathrm{e}^{-\alpha t} + B.\mathrm{e}^{-\beta t} + D.\mathrm{e}^{-\gamma t} \tag{27}$$

Figure 11 shows the plasma concentrations of fentanyl following a single i.v. dose (from Hull and McLeod, 1976), with the best possible bi-exponential curve fit. Figure 12 shows the same data points with a three-exponential curve fit, which is obviously much more satisfactory. Great care must be exercised when expanding the number of terms, since the "degrees of freedom" in the regression equations are progressively reduced, thus widening the confidence interval for the line. This means that although the more complex curve may fit the points better, the *probability* of it being right diminishes. The number of terms must not exceed that which can be statistically justified but, at the same time, the data should not be "forced" to fit too simple a model.

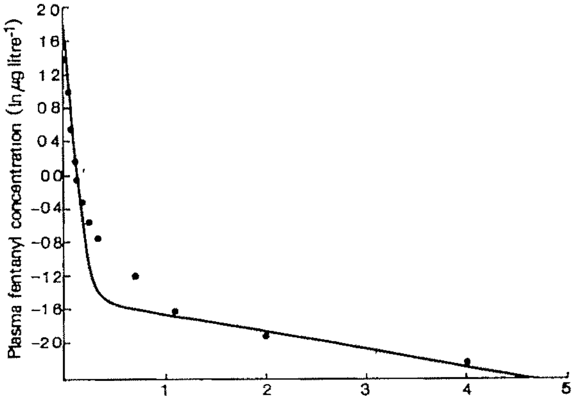


FIG. 11. Plasma concentrations of fentanyl following a 50-µg i.v. injection, with a bi-exponential fitted curve (semi-logarithmic ordinates). It is evidently unsatisfactory.

Figure 13 shows the derived three-compartment model which corresponds to the three-exponential

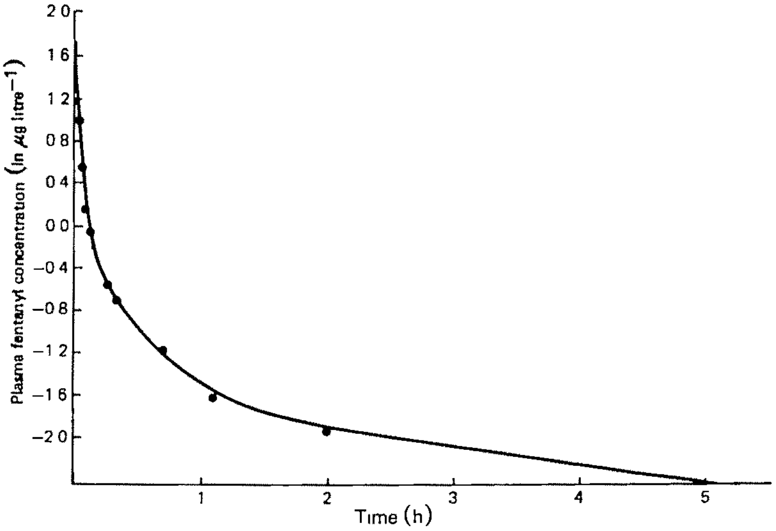


FIG. 12. The data of figure 11 replotted, with an optimal three-exponential curve fit. (From Hull and McLeod, 1976.)

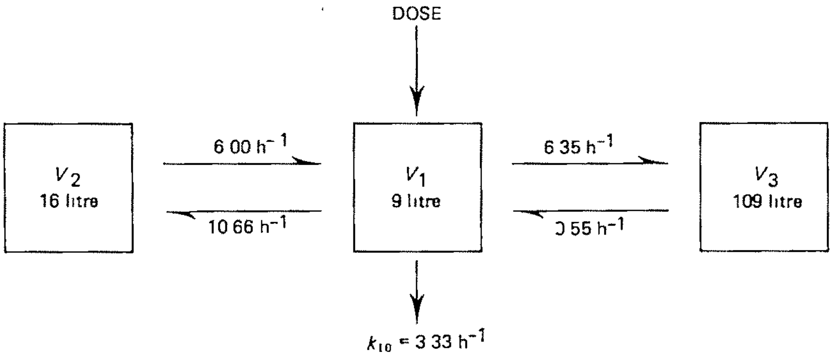


FIG. 13. A three-compartmental model derived from the three-exponential curve in figure 12. (From Hull and McLeod, 1976.)

curve in figure 12. (This is a "mamillary" model, in which both peripheral compartments connect to compartment one. A "catenary" model, which has been proposed for some drug metabolites, has V_3 "deep" to V_2, but not connected to V_1 at all, and has quite different characteristics.)

It can be seen that the smooth decay curve of this model is the result of the presence of compartment two, which has characteristics intermediate between those of compartments one and three.

Drug concentrations in all three compartments following a single dose are shown in figure 14. The curves are computed by repeated solution of the three exponential equations characterizing C_1, C_2 and C_3 for progressive values of t. They are analogous to those for the two-compartment model, but can only be derived by somewhat arduous mathematics. (For a detailed analysis, see Hull et al., 1978.) Three-compartment characteristics have also been ascribed to tubocurarine (Gibaldi, Levy and Hayton, 1972) and to diazepam (Kaplan et al., 1973).

More complex models

Only rarely can a plasma decay curve be defined so precisely as to permit the justification of more than three exponential terms, so that models derived from such curves are necessarily very simple. Moreover,

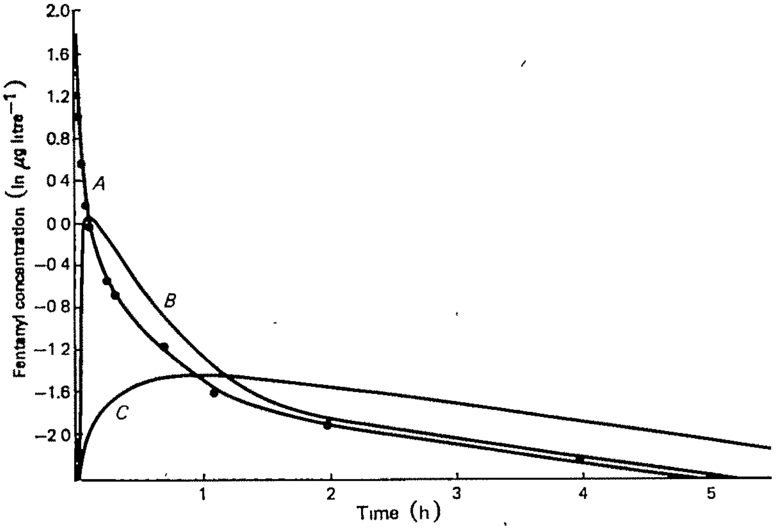


FIG. 14. Drug concentrations in all compartments of the model of figure 13, following a 50-μg dose into the central compartment. (From Hull and McLeod, 1976.)

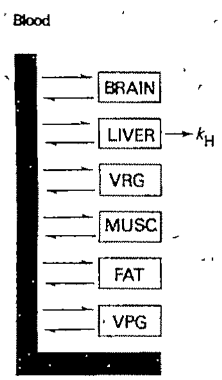
the compartments cannot be reconciled with anatomically *real* volumes. Thus a two-compartment model derived from a "washout curve" *could* predict the plasma concentrations which would be likely to result from an i.v. bolus followed by an infusion of any desired rate. It could *not* predict the probable consequences, in model terms, of the reduction in cardiac output following a large haemorrhage, because cardiac output and blood volume are not parameters of the model.

This limitation can be overcome by the development of *perfusion* models, which are much more "realistic" in the physiological sense, but require a good deal more information. The perfusion model takes a number of compartments, which are now anatomically identifiable, and by consideration of their volumes, blood flow rates, and tissue–blood partition coefficients (λ), computes the movement of drug between them. The model is thus limited only by the number of identifiable "tissue units" on which the kineticist has reliable data.

Drug is assumed to exchange between plasma and "tissue" according to first-order kinetics, with the rate constants determined by the perfusion rate. This simple concept is complicated by the fact that different drugs have a wide range of solubilities in the various tissues, and therefore widely varying tissue–blood partition coefficients. (Thiopentone, for instance, has $\lambda = 1.4$ for brain, but $\lambda = 11.0$ for fat (Price 1960).) After a period of infusion, the concentration (g litre^{-1}) in fat will be much greater than in plasma, so that it is evident that movement is not determined by a simple concentration gradient, but by a "tension" gradient analogous to that which determines the rate of transfer of dissolved gases.* Consider the simple perfusion model for thiopentone described by Saidman and Eger (1966), which is summarized in figure 15. The body is divided into seven compartments, the *volumes* of which are determined by direct measurement. To each compartment is ascribed a *partition coefficient* (λ) which describes the ratio of quantities of drug which would lie in equal volumes of tissue and blood *at equilibrium*. (Thus, at equilibrium, 1 g of fat contains 11 times as much thiopentone as 1 g of blood.) The tissue *space* into which drug distributes is, therefore, the product of the anatomical volume and the tissue–blood partition coefficient. If the compartment is now considered to have a *distribution volume* equal to this computed space, the model will behave in exactly the same way as a simple compartmental system having first-order kinetics (i.e. drug moving along concentration gradients). However, it *must* be remembered that the "concentrations" which now appear in each compartment are really "tensions", and must be

---

* Drug molecules will move so as to equalize the *chemical potential* throughout a system, so that the rate of movement is proportional to the chemical potential gradient. Since "tension" is, for dissolved gases, a direct function of chemical potential, we will retain the term for other molecules also. It does, however, have the dimension of *concentration* rather than pressure.



Blood flow (litre min⁻¹)	λ	Volume	"Space"
0 7	1 4	1 3	1 82
1 5	1 9	1 5	2 85
3 2	1 5	3 2	4 8
1 0	1 5	33	49 5
0 32	11	14 5	159 5
0 075	1.5	12 5	18 75
5 0	1 0	–	–

FIG. 15. A perfusion model for thiopentone. (From data of Saidman and Eger, 1966.) VRG = vessel rich group; VPG = vessel poor group; MUSC = muscle. The partition coefficient (λ) expresses the ratio of drug concentrations in tissue and blood at equilibrium. The product of partition coefficient and anatomical volume (litre) yields the drug "space", which has the dimension of volume (litre).

multiplied by the partition coefficient to obtain the concentrations which would actually occur. It should be evident by now that the "spaces" in a perfusion model are directly analogous to the compartments of a simple kinetic model, and are simply dividing up the same total volume in a different way. The sum of all the "spaces" should therefore equate with the steady-state distribution volume (V^{ss}). A similar model for lignocaine (Benowitz et al., 1974a) tested this hypothesis by constructing both models for the same subjects. Their finding of $V^{ss} = 0.90$ litre kg^{-1} and $\Sigma[V.\lambda] = 0.92$ litre kg^{-1} suggests identity between the two volumes. The rate constants for the perfusion model are simply derived from the blood flows (measured or estimated) to the various tissue units.

The perfusion model is infinitely more flexible than the simple kinetic model, as it is possible to simulate the effects of physiological changes, as in Benowitz and colleagues (1974b) and Mapleson (1977). It must, however, be stressed that the quality of *output* is only as reliable as that of the *input*, so that perfusion models are only of value when a great deal of information concerning the distribution characteristics of the drug are available. Only rarely, as in the quoted studies, is this so.

INFUSION KINETICS

It is instructive to consider the effect of a constant-rate drug infusion on the models already described, since many anaesthetic agents are administered in this way.

The one-compartment model

When infused, drug concentration increases in the form of a wash-in exponential curve, according to the expression:

$$C = [k'/(V.k)](1 - e^{-kt}) \qquad (28)$$

where k' is the drug infusion rate (i.e. the zero-order dose infusion rate constant, which has the dimension of mass per unit time).

Figure 16 illustrates the predicted result of a constant rate infusion into the BSP model of figure 6.

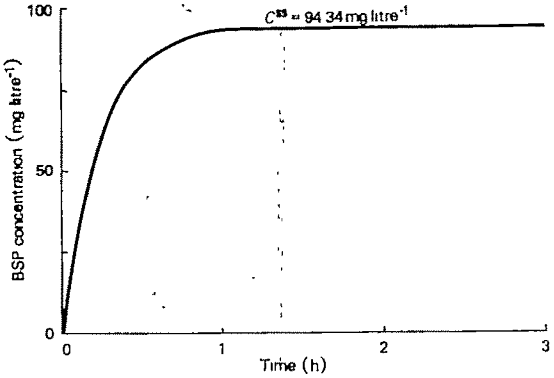


FIG. 16. A first-order "wash-in" curve (equation (28), above), predicting the response of the one-compartment BSP model to a constant infusion. Infusion rate (k') = 50 mg h^{-1}.

Wash-in exponential curves approach a steady-state final concentration, or asymptote at $t = \infty$ but, as in the more familiar wash-out curve, reach 98% of it in 4 time constants. The steady-state concentration C^{ss} can easily be derived from equation (28), since $(1 - e^{-kt}) = 1$ at $t = \infty$.

$$\text{Thus at } t = \infty,\ C^{ss} = k'/(V.k) \qquad (29)$$

This is, of course, a linear equation, in which C^{ss} is directly proportional to the infusion rate. Since the product $V.k$ = clearance, equation (29) can be further clarified as

$$C^{ss} = k'/Cl \qquad (30)$$

that is, the simple ratio of dosage to clearance.

If, at equilibrium, the infusion is stopped, the concentration declines simply according to the expression:

$$C = [k'/(V.k)](e^{-kt}) \qquad (31)$$

which is the wash-out equivalent of equation (28).

It is of course perfectly possible to calculate C during recovery from an infusion which has *not* reached equilibrium, by a combination of equations (28) and (31).

It is often clinically desirable to attain C^{ss} as quickly as possible, and then to maintain it by infusion. This is most easily achieved by an initial loading dose.

Now since concentration = dose/volume, it follows that loading dose Xd = desired concentration × volume, that is,

$$Xd = C^{ss}.V \tag{32}$$

The maintenance infusion rate is readily obtained by rearrangement of equation (29), so that

$$k' = C^{ss}.V.k \tag{33}$$

Thus a dose of $(C^{ss}.V)$ followed by $(C^{ss}.V.k)$ per hour will, theoretically at least, yield an immediate and constant drug concentration of C^{ss}.

Figure 17 shows how a bolus infusion can be applied to the BSP model to achieve a "target concentration" of 100 mg litre^{-1}.

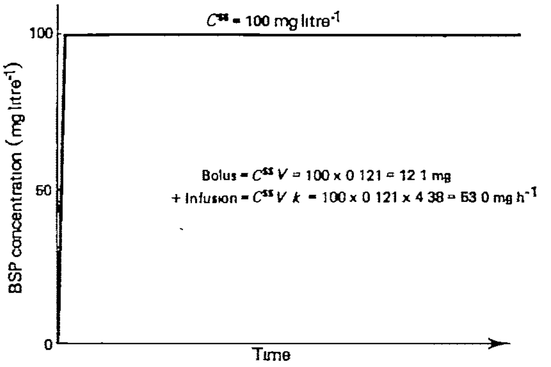


FIG. 17. A bolus+infusion regime calculated to yield an immediate and constant concentration of 100 mg litre^{-1} in the one-compartment BSP model (fig. 6).

The two-compartment model

The infusion characteristics of the two-compartment model are of course much more complicated, as redistribution takes place as well as elimination. The wash-in curve is broadly analogous to that for a one-compartment model (Gibaldi and Perrier, 1975):

$$C_1 = \frac{k'_{01}}{V_1.k_{10}}\left(1+\frac{\beta-k_{10}}{\alpha-\beta}\,e^{-\alpha t}+\frac{k_{10}-\alpha}{\alpha-\beta}\,e^{-\beta t}\right) \tag{34}$$

Since, however, the functions $e^{-\alpha t}$ and $e^{-\beta t}$ become insignificant as $t \to \infty$, this ponderous equation simplifies at steady state to

$$C^{ss} = k'_{01}/(V_1.k_{10}) \tag{35}$$

which is, of course, directly analogous to equation (29).

The infusion rate (k'_{01}) required to achieve a required value (C^{ss}) is therefore, as in the one-compartment model:

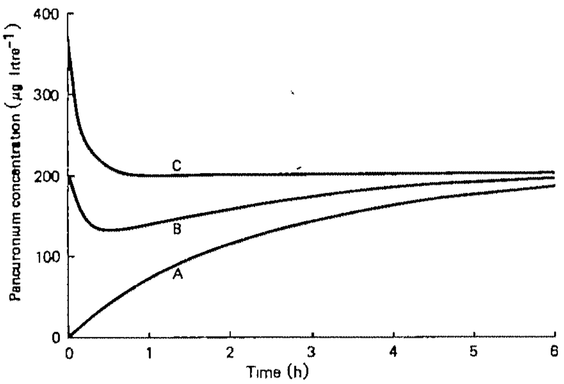


FIG. 18. Predicted drug concentrations in the central compartment of the two-compartment pancuronium model of figure 9. In order to attain a constant concentration of 200 µg litre^{-1}, a simple infusion (line A) can be given, but C^{ss} is reached most quickly by giving an initial bolus dose based on the apparent distribution volume (line C). At the expense of a slower approach, C^0 can be limited to the "target concentration" by giving a smaller bolus (line B). Line A = infusion only: $k'_{01} = C^{ss}V_1k_{10}$ = 1011 µg h^{-1}; line B = infusion+bolus: bolus dose = $C^{ss}V_1$ = 1360 µg; line C = infusion+bolus: bolus dose = $C^{ss}V^{\beta}$ = 2510 µg.

$$k'_{01} = C^{ss}.V_1.k_{10} \tag{36}$$

or (fig. 18, line A)

$$k'_{01} = C^{ss}.V^{\beta}.\beta \tag{37}$$

This simplification should come as no surprise: at steady state no drug is entering or leaving compartment two, so the model *behaves* as it if were not there (i.e. a one-compartment model where $V = V_1$).

It is *possible* by consideration of the *rate of increase* of plasma concentration during an infusion, to derive the parameters of the two-compartment model. This technique can be useful when it is not practicable to give a single bolus dose of sufficient size (i.e. because of narrow therapeutic range, presence of concentration-related side-effects, etc.). In the case of rapidly redistributed drugs such as fentanyl, the α phase after a bolus dose can be very difficult to characterize, as a result of inhomogeneity of plasma concentration during the first few recirculations; so the infusion method may offer distinct advantages to the clinical investigator.

Declining drug concentrations after stopping the infusion *can* be calculated (whether or not equilibrium has been reached) but the equations are even more complex than (34), and so are not reproduced here. As in the one-compartment model, a steady-state concentration can most *rapidly* be attained by an initial loading bolus dose. The choice of dose is, however, a little more difficult. From equation (32) we can say that the dose should be the product $C^{ss}.V$; but which V? If the initial distribution volume V_1 is chosen, C^{ss} will indeed be reached immediately (fig. 18, line B) but unfortunately will not be sustained, since drug will be rapidly redistributed to V_2. If, on the other hand, the apparent distribution volume (V^{β}) is used, so that the dose is increased to the product $C^{ss}.V^{\beta}$, the initial concentration will be much greater than required (fig. 18, line C), but will *decline* to the C^{ss} value. The high initial concentration may be clinically undesirable, so a compromise value between $C^{ss}.V_1$ and $C^{ss}.V^{\beta}$ may be preferable.

An alternative approach is to give the larger dose ($C^{ss}.V^{\beta}$) as a short infusion, to allow some redistribution to take place as it is given and thus minimize the initial peak.

PROTEIN BINDING

Many drugs form complexes with both plasma and tissue proteins. The bonds are generally reversible, and conform to the law of mass action:

$$\underset{\text{drug}}{[\text{D}]} + \underset{\text{protein}}{[\text{P}]} \underset{k_{\text{BF}}}{\overset{k_{\text{FB}}}{\rightleftharpoons}} \underset{\text{complex}}{[\text{DP}]}$$

The association and dissociation processes take place very quickly, and can generally be considered to be instantaneous. The equilibrium association constant K_{A} is defined as the ratio of rate constants, and of bound to the product of unbound concentrations:

$$K_{\text{A}} = \frac{k_{\text{FB}}}{k_{\text{BF}}} = \frac{[\text{DP}]}{[\text{D}].[\text{P}]} \qquad (38)$$

This simple relationship is often obscured by the fact that one protein molecule may possess several binding sites for a particular drug, which may or may not have the same association constant.

It can generally be assumed, however, that so long as the plasma proteins remain unchanged, the ratio of "free" to "bound" drug will remain constant. This ratio depends upon the nature of the drug molecule. Small, neutral, water-soluble molecules such as ethyl alcohol will not bind to protein at all, whereas larger, lipophilic molecules may exhibit very high binding ratios. Some (such as warfarin and phenylbutazone) are more than 99% bound to plasma proteins (Rowland, 1978).

Since the number of binding sites is limited by the plasma protein concentration, it might be expected that [P] in equation (38) would diminish as [DP] increases with increasing drug concentration. In practice, this is rarely so, since the binding sites usually exceed greatly the number of drug molecules. Only when drug concentrations are great (as in the case of therapeutic doses of salicylates) will [D] be large enough to alter [P] significantly. For the same reason, displacement of one drug from its protein-binding sites by another will only occur to an appreciable degree when concentrations are very great, and [P] reduced.

We must now consider the degree to which protein binding must be taken into account when constructing a kinetic model.

Protein-bound drug can be considered to constitute a subdivision of the central compartment, with drug moving isotropically according to the usual pair of rate constants (fig. 19). k_{FB} and k_{BF} are, however, very rapid, so that, as stated above, the two volumes can be considered to be in constant equilibrium. Protein-bound drug is generally pharmacologically inert and must become unbound before redistribution or elimination can take place. It is therefore the free concentration (C_f) which determines the rate of transfer to compartment two. Since the "free" and "bound" fractions of the central compartment are in constant equilibrium, they can in fact be considered to be *one*, so long as the distribution volume is correctly calculated.

Consider the "pancuronium" example. Based on a bi-exponential decay of plasma concentration ([D]+[DP]), the central compartment (V_1) of the model was calculated to have a volume of 6.8 litre and V_2 a volume of 5.2 litre. If we now assume that plasma pancuronium is 80% protein bound (Thompson,

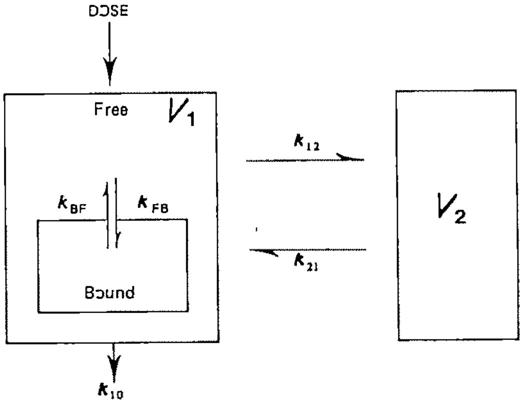


FIG. 19. A two-compartment model developed to include a V_1 subcompartment for protein-bound drug.

1976), it follows that "free" pancuronium will constitute only 20% of the whole. If the free concentration is only 20% of the "total" value, then the model must be recomputed for the change, which is a five-fold increase in volume. Figure 20 shows the modified model. V_1 now includes an internal subcompartment representing bound drug, and the parameters of the model recalculated for the 80% reduction of "exchangeable" plasma pancuronium.

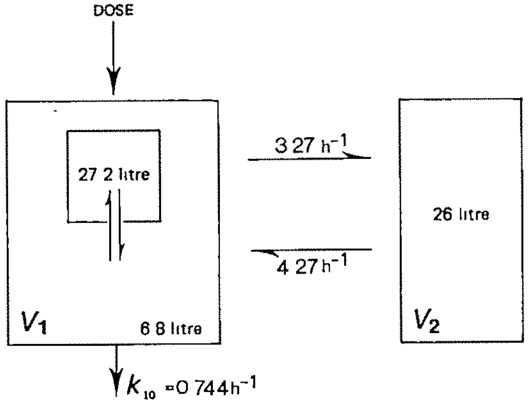


FIG. 20. A modified model for pancuronium, assuming 80% protein binding in the central compartment.

The rate constants are unchanged. This approach to compartmental analysis is essential if drug concentrations in compartments other than V_1 are to be estimated (as in Hull et al., 1978). Even when the site of drug action is in the central compartment itself, protein binding must be taken into account, since, in the case of drugs which are highly protein-bound, a small change in the binding ratio may have a profound effect upon the effective "free" drug concentration.

BIOPHASE KINETICS

The site at which a drug exerts its principal pharmacological effect can be termed the *biophase* (Furchgott, 1955). Drug molecules usually reach the biophase by passive diffusion along a concentration gradient from the plasma, which can be assumed to be part of the initial distribution volume (central compartment). When the *free* (unbound) drug concentration in the plasma decreases below that in the biophase the process is reversed, so that drug re-enters the plasma, thus terminating the effect. Drug molecules in the biophase may (Furchgott, 1955):

(1) remain freely dissolved in the biophase,
(2) bind to specific receptors, thus exerting the *effect*,
(3) bind to non-specific, inactive sites such as tissue proteins,
(4) undergo biotransformation without returning to the plasma,
(5) be excreted without returning to the plasma,
(6) return unchanged to the plasma.

The degree to which drug binds to a specific receptor thus depends, not upon a simple diffusion equilibrium, but on a complex array of competing influences which may defy analysis (Waud, 1968).

The relative importance of the various factors will obviously depend upon the tissue concerned. For instance, biotransformation and excretion are more likely to occur in liver cells than at the neuromuscular junction!

Since in *most* cases drug in the biophase can be thought of as being a continuous equilibrium with specific receptor sites, it is apparent that the rate of increase of biophase drug concentration is a limiting step in the drug's onset characteristic. This plasma-biophase rate constant is determined (Riegelman, Loo and Rowland, 1968) by:

(a) perfusion of the "target" tissue,
(b) tissue–blood partition coefficient,
(c) distance over which drug must diffuse,
(d) diffusibility of the drug molecule.

Consider some examples, which illustrate the principles involved. Sodium nitroprusside is a small, soluble and highly diffusible molecule, which acts directly on arteriolar smooth muscle. The onset time is extremely short and is probably no more than the time taken for transport within the plasma volume. The biophase rate constant must therefore be very great, and for practical purposes can be disregarded, so that the biophase should be considered to be an integral part of the initial distribution volume.

An elegant experiment on rats (Giarman and Roth, 1964) provides direct evidence of a relatively slow biophase rate constant. These authors injected rats i.v. with GHB (γ-hydroxybutyric acid), and measured the times at which the animals fell asleep and awoke, serial plasma concentrations and serial brain concentrations. They found that, after injection, the rats fell asleep at 8–12 min and awoke at 80 min. At these times the plasma concentrations differed widely, but in each case the brain concentration was approximately the same. They concluded that, since a brain concentration of 70 $\mu g\ g^{-1}$ appeared to be the anaesthetic "threshold", the rate of diffusion between plasma and brain was a determining factor and responsible for the onset latency. The results of this study are in accord with the biophase concept, and suggest that the measured brain concentrations were a good estimate of biophase concentration.

A more indirect, but nevertheless interesting, study was discussed by Wagner (1971). Five healthy volunteers were given i.v. injections of LSD (d-lysergic acid diethylamide), and their plasma concentrations and ability to do mental arithmetic were followed for 8 h. The drug concentrations decreased bi-exponentially, allowing construction of a simple two-compartment model. The mental performance scores correlated very poorly with plasma concentrations, but very well with the computed concentrations in compartment two, with both variables maximizing at approx. 30 min. It is evident that the LSD biophase has a *slow* rate constant, similar to that of the peripheral compartment of the model.

A biophase model for pancuronium has been proposed (Hull et al., 1978), which suggests that although the rate constant is fast, it cannot be disregarded when attempting to reconcile plasma concentrations with measured twitch depression.

It should now be evident that it is futile to attempt correlations between plasma concentration and pharmacological effect unless: (a) the biophase rate constant is demonstrably *very* rapid or (b) the biophase rate constant can be *estimated* by simultaneous consideration of both model parameters and measured effect (Wagner, 1971; Hull et al., 1978) or (c) drug is administered as a constant-rate infusion for many half-lives, so that it is safe to assume that free drug concentrations in both plasma and biophase are identical.

PHARMACODYNAMICS

The "pharmacodynamic" relationship between biophase drug concentration and its site of action (often a specific receptor) provides a rich source of variation in response, which is *superimposed* on that resulting from pharmacokinetic mechanisms.

Classical receptor theory (Stephenson, 1956) assumes that drug molecules bind reversibly with a limited number of identical *receptor sites* in order to exert an effect; the effect ceasing when dissociation occurs. (The process is directly analogous to the *Michaelis–Menten* model for enzyme kinetics.)

Thus,

$$\underset{\text{drug}}{[\mathrm{D}]} + \underset{\text{receptor}}{[\mathrm{R}]} \underset{k_{\mathrm{RD}}}{\overset{k_{\mathrm{DR}}}{\rightleftharpoons}} \underset{\text{complex}}{[\mathrm{DR}]}$$

At equilibrium,

$$K_{\mathrm{D}} = \frac{k_{\mathrm{RD}}}{k_{\mathrm{DR}}} = \frac{[\mathrm{D}].[\mathrm{R}]}{[\mathrm{DR}]} \tag{39}$$

where K_{D} is the dissociation constant.

This equation can be manipulated to express the concentrations in terms of the ratio of occupied receptors [DR] to the sum of bound and unbound receptors $[\mathrm{R_T}]$ where $[\mathrm{R_T}] = [\mathrm{R}] + [\mathrm{DR}]$, so that

$$\frac{[\mathrm{DR}]}{[\mathrm{R_T}]} = \frac{[\mathrm{D}]}{[\mathrm{D}] + K_{\mathrm{D}}} \tag{40}$$

The ratio $[\mathrm{DR}]/[\mathrm{R_T}]$ is usually referred to as *receptor occupancy*, and given the symbol Y. Thus,

$$Y = \frac{[\mathrm{D}]}{[\mathrm{D}] + K_{\mathrm{D}}} \tag{41}$$

(This simple hyperbolic relationship is often referred to as the "Langmuir curve", although Langmuir's original work (1918) was in the field of gas adsorption onto plane surfaces. The situations are, however, surprisingly analogous.) From equation (41) it can be deduced that when exactly 50% of receptors are occupied ($Y = 0.5$), then $K_{\mathrm{D}} = [\mathrm{D}]$. Since under these conditions K_{D} is numerically equal to [D], it can, like the Michaelis constant, be given the dimension of concentration. (The reciprocal of K_{D} (i.e. the association constant) is frequently referred to as the *affinity* of the drug for the receptor.) K_{D} has been determined experimentally for many drugs; for instance, the values for pancuronium and tubocurarine have been estimated to be 25.1 and 34.5 nmol litre^{-1} respectively (Bowen, 1972; Waud, Cheng and Waud, 1973).

Figure 21 shows equation (41) solved for $K_{\mathrm{D}} =$ 25.1 nmol litre^{-1}, which can be seen to be the concentration at which equal numbers of receptors are occupied and unoccupied. The hyperbolic function appears as a sigmoid curve when occupancy is plotted against log-concentration. If the measured *effect* of the drug were directly proportional to receptor occupancy, the log-concentration/effect characteristic would be linear over a fairly wide range (20–80% occupancy). Since the plasma concentrations of many drugs decline exponentially (at least during the elimination phase), one would therefore expect the *effect* to decline *linearly* at the same rate, regardless of dose. Although in some cases this undoubtedly occurs (fig. 22 (Levy, 1967)), Waud (1968) has pointed out that this simple relationship is often fortuitous, and is in fact much more complex. That for tubocurarine is a case in point, since it has been shown (Paton and Waud, 1967) that mammalian

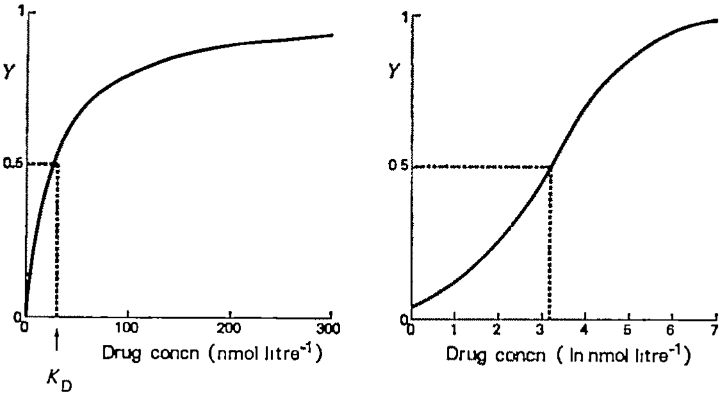


FIG. 21. Assuming K_D = 25.1 nmol litre^{-1}, receptor occupancy Y is plotted as a function of drug concentration (equation (41)), on both linear and semi-logarithmic ordinates. If the intensity of effect were proportional to occupancy, then effect would be proportional to log concentration over a fairly wide range (20–80%).

striated muscle is unaffected by 70% receptor occupancy (the margin of safety), but fully paralysed by 90%. Moreover, it appears likely that the "margin of safety" for diaphragm receptors is appreciably greater than for those in limb muscles (Waud and Waud, 1972).

Classical receptor theory is now accepted to be an oversimplified view of the mechanisms involved, and the relationships between occupancy and effect are often obscure (Colquhoun, 1973).

Concentration–response relationships are difficult to quantify *in vivo* because pharmacological, physiological and chemical synergists and antagonists may all interact to modulate the final response (Rawlins, 1974). Figure 23 summarizes some of the factors which may contribute to the variation in response to pancuronium.

The clinical anaesthetist may, if he has persisted this far, be forgiven for feeling that the sources of variation are so legion that in the case of many drugs used in anaesthetic practice it is better to titrate dose against response than to attempt to predict the correct

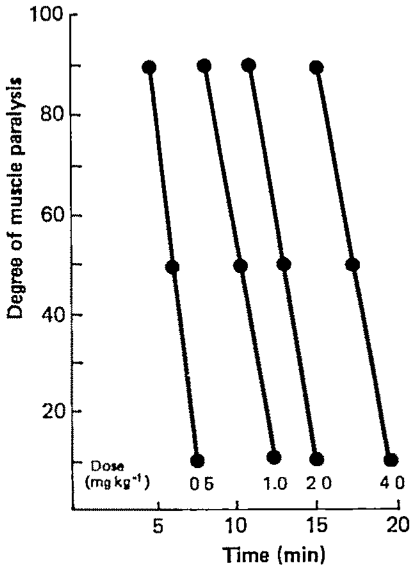


FIG. 22. Recovery from suxamethonium paralysis in man occurs at the same rate, regardless of original dose, thus supporting the hypothesis that effect is proportional to receptor occupancy. (From Levy (1967), reproduced by permission of the author and editor of *Journal of Pharmaceutical Sciences*.)

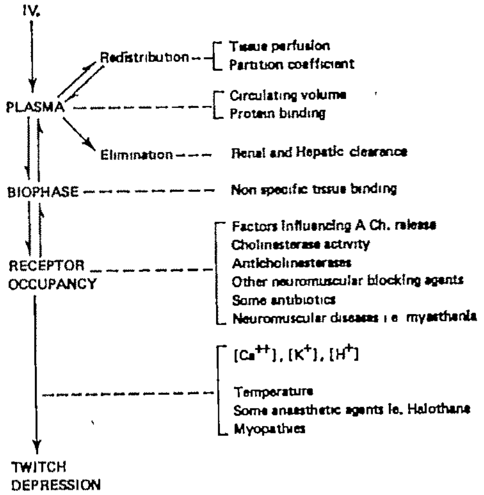


FIG. 23. Some factors determining the variation in response to a neuromuscular agent such as pancuronium.

dose on theoretical grounds. He is, of course, right, but a clear understanding of the ways in which his patient's "drug model" may be influenced by physiological or pathological changes will enable him to anticipate variations in drug requirement, and therefore "titrate" with greater insight and delicacy.

APPENDIX

SYMBOLS AND ABBREVIATIONS

A, B, D α, β, γ	Constants characterizing a multi-exponential decay
C	Concentration of drug at time t
C_1, C_2 etc.	Concentration of drug in compartments one, two etc. at time t
C^0	Concentration of drug at time zero
C_f	Concentration of free (unbound) drug at time t
C_1^{ss}	Concentration of drug in compartment one at steady state
Cl	Clearance
[D], [P], [DP]	Terms in a mass-action equation representing concentrations of drug, protein, and drug–protein complex molecules
[D], [R], [DR]	Terms in a mass-action equation representing concentrations of drug molecules, receptors, and drug–receptor complexes
e	2.718 . . ., the base of the natural logarithm (expressed to three decimal places)
exp	Synonymous with e^x, the anti-natural logarithm
k	First-order rate constant in a one-compartment model
k'	Zero-order rate constant for a drug infusion into a one-compartment model
k_{21}, k_{12}, etc.	First-order rate constants in a multi-compartment model. k_{21} characterizes the movement of drug from compartment two to compartment one, and k_{12} *vice versa*
k_{10}	First-order elimination rate constant from compartment one of a multi-compartment model
k'_{01}	Zero-order (i.e. constant rate) drug infusion rate-constant into the central compartment (V_1) of a multi-compartment model
k_R, k_H	First-order elimination rate constants by renal and hepatic routes
k_{FB}, k_{BF}	Association and dissociation rate constants for the drug–protein mass-action equation
k_{DR}, k_{RD}	Association and dissociation rate constants for the drug–receptor mass-action equation
K_A	Association constant for the protein binding mass-action equation
K_D	Dissociation constant for the drug–receptor mass-action equation
λ	Tissue–blood partition coefficient
ln	Natural logarithm
n	Number of compartments in a multi-compartment system
P, Q	Constants determining the bi-exponential characteristics of compartment two in a two-compartment model
$[R_T]$	Total concentration of receptors
t	Time (h)
$T_{\frac{1}{2}}$	Half-life
$T_{\frac{1}{2}}^{\beta}$	Half-life of the terminal (β) phase of a bi-exponential decay
τ	Time constant
V	Apparent volume of distribution for a one-compartment model
V_1, V_2, etc.	Compartmental volumes in a multi-compartment model
V^{β}	Apparent distribution volume of a two-compartment model during the elimination (β) phase
V^{ss}	Steady-state distribution volume
Xd	Mass of drug given as a bolus
X^{ss}	Mass of drug in body at steady state
Y	Receptor occupancy

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DRUG–RECEPTOR REACTIONS

J. NORMAN

Many drug molecules are small in size when compared with the molecules in the cell membranes with which they interact. The results of the combinations vary: membrane permeability may change, second messengers such as cyclic adenosine monophosphate may be produced or the cell may start to synthesize new protein. The actions of many drugs either mimic or alter the effects of naturally occurring transmitters produced by the nervous or endocrine systems. In order to understand the quantitative aspects of the relationships between the amounts of drug administered and the effects produced there are a number of models which describe these relationships. Hull (1979) describes elsewhere in this issue how the drugs are brought to and eliminated from the active sites; this paper aims to describe the relationship between the amount of drug at the site and the subsequent action.

The first model will look at the simplest case where one molecule of drug reacts with one of receptor. Receptor is used as an abbreviation for the component of the cell to which the drug binds. Many actions of agonist and antagonist drugs can be described by this model. The other model examined assumes the receptor to be composed of a number of subunits. With such subunits there is the possibility that they can interact and that the combination of drugs with the subunits can alter the interactions.

Whilst the paper is principally concerned with drugs and receptors, there are other similar systems in the body where small and large molecules interact. Oxygen is transported by haemoglobin—a protein consisting of four subunits (Perutz, 1978). Similarly, enzymes act on substrate moledules which usually are relatively small. The model described for drug–receptor reactions can be applied to these events also.

ONE DRUG–ONE RECEPTOR MODEL

The classic model developed by Langley (1907) and Clark (1933) described the situation in which one molecule of drug reacts with one of receptor. In order to determine what the effect of any given concentration of drug will be we first have to calculate what fraction of all receptor molecules present will be occupied by the drug. For simplicity we will then assume that the effect produced will be directly proportional to that fraction.

Suppose the reaction is:

$$D+R \rightleftharpoons DR$$

where D stands for drug, R for receptor and DR for the combination. The Law of Mass Action can be applied and, at equilibrium, the rates of combination and dissociation are the same. We can then write:

$$\frac{[D]\,[R]}{[DR]} = K \qquad (1)$$

where the square brackets denote concentrations expressed as mol litre^{-1} and K is the dissociation constant. (In some texts the equation is inverted and the inverse constant K_b, called the binding constant, is used. Care is needed to ensure which is in use.) High values of K (expressed in units of mol litre^{-1}) show that little binding of the drug occurs, whilst with low values the drug will be strongly bound. In order to calculate the fraction of all the receptors (a total concentration of R_t) that have drug bound, the following development is needed:

$$R_t = [R]+[DR]$$

or

$$[R] = R_t-[DR] \qquad (2)$$

This expression for the concentration of free receptors can be substituted into equation (1):

$$[D]\,(R_t-[DR]) = K[DR]$$

and

$$[D]\,R_t-[D]\,[DR] = K[DR]$$

and

$$[D]R_t = [DR]\,(K+[D]).$$

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Finally,

$$\frac{[\mathrm{DR}]}{\mathrm{R_t}} = \frac{[\mathrm{D}]}{[\mathrm{D}]+K} \qquad (3)$$

The left-hand side of the equation gives the fraction of all the receptors ($\mathrm{R_t}$) which have drug bound (DR). If the effect (E) produced by the drug is directly proportional to this fraction, we can use a graph to relate the effect to the drug concentration (fig. 1A). The curve is a rectangular hyperbola. When the effect is half the maximum that can be obtained the drug concentration has the same value as the dissociation constant K.

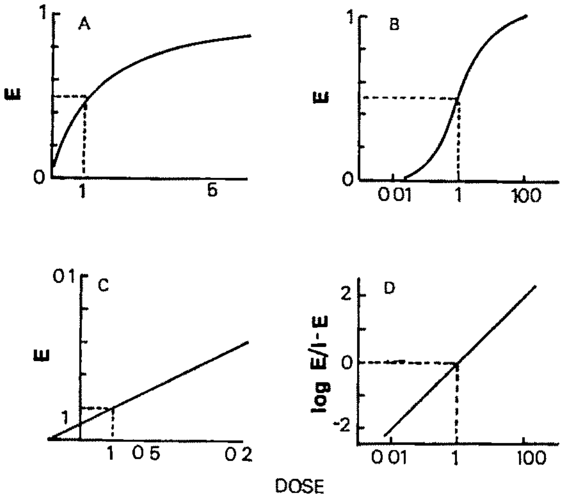

FIG. 1. Dose–response curves. Abscissae—doses in arbitrary concentration units. Ordinates—effects assumed to be proportional to receptor occupation. A: the rectangular hyperbola relating effect to concentration. B: the log dose–response curve. C: the Lineweaver–Burke plot of the reciprocal of the effect *v.* the reciprocal of the dose. D: the Hill plot of the logarithm of $E/1-E$ *v.* the logarithm of the dose. The broken lines show the 50% response—at these responses the drug concentrations are equivalent to the dissociation constants.

There are problems with graphical plots such as figure 1A. One is that it is difficult to show the effects of more than a small range of drug concentrations. It is more usual to use the relationship between the effect and the logarithm of the drug concentration. Figure 1B shows the picture which is now a sigmoid curve. (Most texts use logarithms to the base 10 but natural logarithms can be used just as easily—see Hull, 1979.)

There are other transformations of the dose–response curve which give straight lines; two are shown in figures 1C and 1D. Figure 1C shows the Lineweaver–Burke plot which is more commonly used in biochemical studies. The effect measured is the rate of the reaction and is expressed here as a fraction of the maximal velocity. The graph plots the reciprocal of this fraction against the reciprocal of the drug or substrate concentration. Thus high reaction rates and high drug concentrations are nearer the axes of the graph. To show how the straight line relationship is reached, equation (3) can be modified. We will assume that the effect (E) is directly proportional to the fractional occupancy of the receptors:

$$\mathrm{E} = \frac{[\mathrm{D}]}{[\mathrm{D}]+K}$$

Invert to

$$\frac{1}{\mathrm{E}} = \frac{[\mathrm{D}]+K}{[\mathrm{D}]}$$

Finally,

$$\frac{1}{\mathrm{E}} = 1+K\frac{1}{[\mathrm{D}]} \qquad (4)$$

In using figure 1C to estimate values for the dissociation constant K, there are statistical problems in that undue emphasis can be given to the effects of low concentration of the drug. Riggs (1963) describes these dangers and offers alternative approaches.

Figure 1D is often described as a Hill plot, in memory of A. V. Hill who first used it in examining haemoglobin (Hill, 1910). The ordinate is the logarithm of the ratio of the fractions of the total receptors occupied by the drug and the fraction not occupied by the drug. If the effect is proportional to the fractional occupancy, then the numerator is (E) and the denominator $(1-\mathrm{E})$ when the maximal action is defined as unity. The expression can be derived from equation (4) by subtracting one from each side:

$$\frac{1}{\mathrm{E}} - 1 = \frac{K}{[\mathrm{D}]}$$

or

$$\frac{1-\mathrm{E}}{\mathrm{E}} = \frac{K}{[\mathrm{D}]}$$

Invert the expression:

$$\frac{\mathrm{E}}{1-\mathrm{E}} = \frac{[\mathrm{D}]}{K}$$

and, taking logarithms,

$$\log\frac{\mathrm{E}}{1-\mathrm{E}} = \log[\mathrm{D}] - \log K \tag{5}$$

The graph will be a straight line with a slope of one. Hill (1910) developed the model further where more than one molecule of drug (oxygen) combines with one of receptor (haemoglobin). Where two drug molecules act with receptor the slope becomes two; with four it becomes four. The oxyhaemoglobin dissociation curve usually shows a value of about 2.7 (Gillies, 1974), suggesting that the simple model will not describe the transport of oxygen.

So far it has been assumed that the effects of the drug are directly proportional to the fraction of receptors occupied. There is evidence that this is not always the case. Waud and Waud (1972) have estimated that at the neuromuscular junction only some 20–25% of all the receptors need to bind acetylcholine to produce a maximal twitch response, a normal train-of-four response needs some 25–30% occupation and a normal tetanic response to stimulation of the nerve at 100 Hz needs 50% occupation. There are thus "spare" receptors. Teleologically, it is advantageous to have spare receptors in that, otherwise, a maximal effect would need a very high concentration of drug or transmitter. The concept of spare receptors only alters the relationship between fractional occupancy and effect and does not alter the model in relating occupancy to drug concentration.

Agonist and partial agonist drugs

Drugs binding to receptors which lead to an effect are called *agonist* drugs. Many drugs may produce the same effect and if this is the result of binding to the same receptors then the *potency* of one drug when compared with another is in effect a comparison of their dissociation constants. A more potent drug has a lower dissociation constant. This only applies to drugs which are capable of producing the maximal effect. *Partial agonists* are drugs which bind but are unable to produce the maximal action even at very great concentrations. Ariens (1964) used the term *intrinsic activity* to relate the occupancy of the receptor by a drug to the effect produced. Full agonists have intrinsic activities of unity and partial agonists have values between zero and one. Drugs which bind but produce no effect have intrinsic activities of zero. Often they interfere with the effects of other drugs, and are *antagonists*.

The effects of antagonists on drug action

Whilst antagonist drugs can also differ in potency and some possess some agonist activity (e.g. practolol and buprenorphine) there seems to be two main classes. *Non-competitive antagonists* block the action of the agonists in such a way that no matter what the concentration of agonist the full action is not seen. The combination of antagonist with the receptor is so strong that dissociation does not occur or the receptor molecule is distorted so as to prevent binding of the agonist. In effect the concentration of receptors free to bind drug is reduced. If half the receptors have antagonist bound the maximal effect of any agonists is reduced by half. Figure 2A shows the effect on the logarithmic dose–response curve.

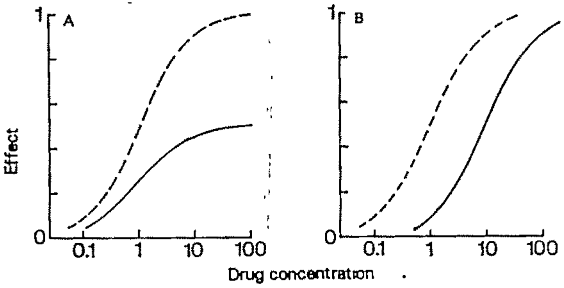

FIG. 2. Antagonist effects. Abscissa—dose of agonist in arbitrary units on a logarithmic scale. Ordinate—effect. The broken line shows the normal response. A: the effect of a non-competitive antagonist in a dose which reduces all responses by half. B: the effect of a competitive antagonist which increases the dose of agonist needed by 10-fold to produce the same effect.

Other antagonists bind reversibly on the receptors and their effects can be surmounted if the concentration of agonist is increased enough. Presumably some of the antagonist–receptor combinations are breaking down and what happens next depends on the relative concentrations of agonist and antagonist and on the strengths of their binding to the receptors. Mathematically we need to know the concentrations of agonist [D] and antagonist [A] and their dissociation constants K_{D}' and K_{A}. For the agonist equation (1) applies and for the antagonists:

$$\mathrm{A}+\mathrm{R} \rightleftharpoons \mathrm{AR}$$

and

$$\frac{[A]\,[R]}{[AR]} = K_A$$

At equilibrium the concentration of free receptors [R] in both equations is the same and we can write:

$$[R] = K_D\frac{[DR]}{[D]} = K_A\frac{[AR]}{[A]}$$

The concentration of receptor binding the antagonist [AR] can now be calculated:

$$[AR] = [DR]\,\frac{K_D}{K_A}\,\frac{[A]}{[D]}$$

The total receptor concentration (R_t) includes the free receptor concentration and those binding the two drugs:

$$R_t = [R] + [DR] + [AR]$$

and, by substitution

$$R_t = [R] + [DR] + [DR]\,\frac{K_D\,[A]}{K_A]\,D]}$$

This can be rearranged to calculate R and, in turn, this can be placed in equation (1):

$$K_D[DR] = \left([D]\,R_t - [DR] - [DR]\,\frac{K_D}{K_A}\,\frac{[A]}{[D]}\right)$$

or

$$K_D[DR] = [D]\,R_t - [D][DR] - [DR]\frac{K_D}{K_A}[A]$$

Collecting all the [DR] terms together:

$$[DR]\left(K_D + [D] + [A]\right)\frac{K_D}{K_A} = [D]\,R_t$$

The fractional occupancy of the receptors by the agonist and hence the effect is then given by

$$\frac{[DR]}{R_t} = \frac{[D]}{[D] + K_D[1 + ([A]/K_A)]} \qquad (6)$$

Increasing the concentration of antagonist or using a more potent antagonist (one with a smaller K_A) both increase the denominator and hence reduce the effect of an agonist. Figure 2B shows that the effect on a logarithmic dose–response curve is to shift the curve to the right but parallel to the original curve.

This parallel shift implies that, in order to get any given effect (say a 50% contraction), the concentration of agonist must be increased by a constant proportion. Schild (1947) introduced the term pA_x to allow a comparison of the potencies of a series of antagonists. With the parallel shift of the logarithmic response curve there will be a concentration of each antagonist which increases the dose of agonist by 10 times to reach the same effect as that seen without antagonists. Using a notation similar to the pH scale for acidity, Schild defined pA_{10} as the negative logarithm of the antagonist concentration which needs a 10-fold increase in agonist concentration. pA_2 is the corresponding value for a two-fold increase in agonist concentration. pA_2 values also indicate the concentration of antagonists numerically equal to the negative logarithm of the dissociation constant for the antagonist. High values for pA_2 are associated with potent antagonists.

MULTIPLE SUBUNIT MODELS

The classic theory developed by Clark (1933) accounts for the responses to many agonists and antagonists, but not to all. There is now much interest in somewhat more complex models in which the receptor is composed of a number of subunits each of which may bind the drug. The essential feature is not the multiple binding of drug but the subsequent interaction of the subunits. When one binds a drug molecule the subsequent change alters the behaviour of the adjacent units. This altered behaviour may show by the altered affinity of the remaining subunits for the drug and also by an altered behaviour of the whole molecule. Imagine that a number of subunits in a membrane receptor surround a central pore. Binding of a drug (or transmitter) might alter the shape of the whole molecule and the pore could become bigger or smaller. The result could be an increase or decrease in the membrane permeability to ions and hence an altered electrical activity of the cell containing that receptor.

Haemoglobin is perhaps the best example of a protein made up of subunits which can bind small molecules such as oxygen and where the binding alters the shape and function of all the subunits (Perutz, 1978). Haemoglobin shows an additional feature of the subunit model. 2:3 Diphosphoglyceric acid binds to the whole molecule at sites other than oxygen, but still producing a decreased affinity of the subunits for oxygen. Such an effect is known as an *allosteric* effect. Allosteric inhibition changes the dose–response in a manner different from those shown in figure 2.

Acetylcholine receptors can now be isolated. Probably they exist as a polymer made up of a number of subunits. Lester (1977) has reviewed the recent evidence showing co-operative behaviour between the subunits and the effects of antagonists and agonists.

There are a number of mathematical models showing how subunits interact and how inhibitors might alter this action. Koshland (1973) has produced a clear account of one in which the binding of one molecule of substrate (or drug) induces a change in the shape of a subunit of the enzyme (or receptor). This change induces changes in the other subunits which can either increase or decrease the affinity of the other subunits for substrate. The mathematics are somewhat complex (see Newsholme and Start, 1973).

In 1965 Monod, Wyman and Changeux described a somewhat simpler system which starts by assuming the receptor (or enzyme or haemoglobin) to be made up of subunits which exist in one of two forms. One is called the tense structure (T) and one the relaxed (R). Let us consider the case where the whole molecule consists of two subunits and that the molecule exists only with both subunits in the T form or the R form. In other words, the molecule can be described as being TT or RR but not TR or RT. Further, let us assume that the molecule only binds drugs when it is in the RR form. When working with drugs it may be that when the drug binds it increases the amount of receptor in the RR form and this may structurally allow an ion gate to open, thereby allowing a change in membrane conductance and so an effect. We would then wish to determine what the concentration of RR was at any given drug dose. Alternatively, with enzymes it may be that substrates only bind to the RR form and we might wish to calculate how many subunits carry substrate and hence are able to change it.

Both calculations involve a number of common steps. We need to know either the fraction of the total receptors in RR forms with or without drug attached *or* the fraction of all the subunits which bind the drug.

Start with the relationship between the tense (TT) and relaxed forms of the receptor (RR) without any drug present. The forms are interconvertible:

$$\mathrm{TT} \rightleftharpoons \mathrm{RR}$$

and at equilibrium, applying the Law of Mass Action:

$$L = [\mathrm{TT}]/[\mathrm{RR}] \tag{7}$$

(The letter L is used conventionally to give this ratio.) Suppose the drug (D) binds only to the R form of the subunit. Further, if the subunits are identical and have the same dissociation constant (K) for the reaction with the drug, we can write for the binding of the first drug molecule:

$$\mathrm{RR}+\mathrm{D} \rightleftharpoons \mathrm{R_D\,R}$$

and

$$\frac{2[\mathrm{RR}]\,[\mathrm{D}]}{[\mathrm{R_D\,R}]} = K$$

and

$$[\mathrm{R_D\,R}] = \frac{2[\mathrm{RR}]\,[\mathrm{D}]}{K} \tag{8}$$

[RR] is the concentration of the RR forms and it is vital to remember that each molecule has two binding sites for the drug. This accounts for the doubling of the effective receptor concentration.

The binding of the second drug molecule is given by

$$\mathrm{R_D\,R}+\mathrm{D} \rightleftharpoons \mathrm{R_D\,R_D}$$

and

$$\frac{[\mathrm{R_D\,R}]\,[\mathrm{D}]}{2[\mathrm{R_D R_D}]} = K$$

Remember that each $\mathrm{R_D\,R_D}$ molecule has two molecules of drug bound to it. We can now calculate the concentration of receptor molecules which has two drug molecules attached to it:

$$[\mathrm{R_D\,R_D}] = \frac{[\mathrm{R_D\,R}]\,[\mathrm{D}]}{2K}$$

and by substituting from equation (8):

$$\begin{aligned}[\mathrm{R_D\,R_D}] &= 2[\mathrm{RR}]\;\frac{[\mathrm{D}]}{K}\frac{[\mathrm{D}]}{2K}\\ &= [\mathrm{RR}]\frac{[\mathrm{D}]^2}{K^2}\end{aligned} \tag{9}$$

Now we must calculate the total concentration of all forms of the receptor ($\mathrm{R_t}$). This must include those forms of the molecule in the tense state (TT) and those in any of the relaxed states (RR, $\mathrm{R_D\,R}$ and $\mathrm{R_D\,R_D}$):

$$\mathrm{R_t} = [\mathrm{TT}]+[\mathrm{RR}]+[\mathrm{R_D\,R}]+[\mathrm{R_D\,R_D}] \tag{10}$$

Expressions derived from equations (7), (8) and (9) can be substituted into this to give:

$$R_t = L[RR]+[RR]+\frac{2[RR]\,[D]}{K}+[RR]\frac{[D]^2}{K^2}$$

or

$$R_t = [RR]\left[L+\left(1+\frac{[D]}{K}\right)^2\right] \qquad (11)$$

The number of receptors in the relaxed form is given by the sum of the RR, R_D R and R_D R_D configurations:

$$\begin{aligned}[RR]+[R_D R]+[R_D R_D] &= [RR]+2[RR]\frac{[D]}{K}+[RR]\frac{[D]^2}{K^2}\\ &= [RR]\left(1+\frac{[D]}{K}\right)^2 \qquad (12)\end{aligned}$$

The fraction of receptors in the relaxed form may be calculated as the ratios of equation (13) to (11). Let it be called Y:

$$\begin{aligned}Y &= \frac{[RR]\left(1+\frac{[D]}{K}\right)^2}{[RR]\left[L+\left(1+\frac{[D]}{K}\right)^2\right]}\\ &= \frac{\left(1+\frac{[D]}{K}\right)^2}{L+\left(1+\frac{[D]}{K}\right)^2} \qquad (13)\end{aligned}$$

This shows the fraction is dependent on the drug concentration and the dissociation constant and also on the ratio of the tense to the relaxed forms of substrate. Provided L does not equal zero, the curve is sigmoid (fig. 3). If L is zero then none of the receptor is in the tense form.

The total amount of drug (or substrate) bound is the sum of the R_D R concentration with twice that of the R_D R_D concentration:

$$\begin{aligned}[R_D R]+2[R_D R_D] &= 2[RR]\frac{[D]}{K}+2[RR]\frac{[D]^2}{K^2}\\ &= 2[RR]\frac{[D]}{K}\left(1+\frac{[D]}{K}\right) \qquad (14)\end{aligned}$$

If the effect such as the metabolic transformation of a substrate is proportional to the amount of substrate bound, the fractional occupancy of the receptor subunits binding drug is given by the ratio of equation (14) to twice that of equation (10) (remember both subunits bind drug):

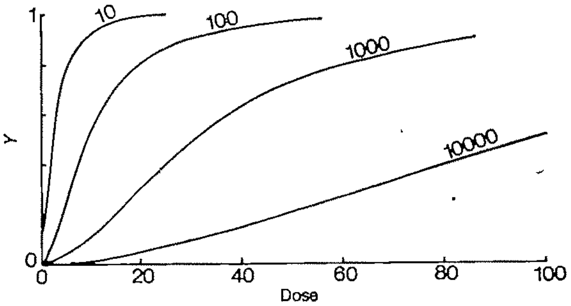

FIG. 3. Dose-response curve when two subunits of receptor co-operate. Abscissa—drug concentration (note the linear scale). Ordinate—fraction of receptors in the relaxed (R) form. From left to right the curve shows the effects of increasing L, the ratio of tense to relaxed forms. An antagonist might act by increasing this ratio.

fractional occupancy =

$$\begin{aligned}&2[RR]\frac{[D]}{K}\left(1+\frac{[D]}{K}\right)\Big/\left\{2[RR]\left[L+\left(1+\frac{[D]}{K}\right)\right]^2\right\}\\ &=\frac{D}{K}\left(1+\frac{D}{K}\right)\Big/\left[L+\left(1+\frac{[D]}{K}\right)^2\right] \qquad (15)\end{aligned}$$

This again will produce a sigmoid curve, provided L does not have a value of zero. If it does, there is no receptor in the tense form and the equation reduces to equation (3), giving a rectangular hyperbola.

Figure 3 illustrates the effects of varying values of L on the curve relating the number of receptors in the relaxed form (equation (13)). When L is large most of the receptors are in the tense form. Low drug concentrations will have little effect in converting the structure to the tense form, but at greater concentrations most of the receptor will be converted. The effect of a sufficient concentration of drug will be to switch most of the receptor to the relaxed configuration which should be the key to the observed action.

Allosteric inhibitors could act on the receptor as a whole or on the subunits and stabilize them in the T form. The effect would be to increase L—the ratio of the tense to the relaxed forms—and move the response curve for the agonist to the right. Figure 3 shows the effect of increasing L.

When there are more than two subunits the mathematics is only slightly more complex. Those interested should read Newsholme and Start (1973).

One important feature of the subunit is that relatively small changes in agonist concentration can have marked changes in the receptor. With the classic model (fig. 2), in order to go from 10% to 90% of the effect it is necessary to change the agonist concentration some 81-fold. In contrast with the simple dimer model (fig. 3), when L is 10 000 then a nine-fold change is all that is needed to go from 10% to 90%. If the receptor is controlling an ion gate small concentration changes will easily change the gate from closed to an open position.

The examination of drug dose–response curves in terms of the classic or more complex subunit models is valuable in identifying some of the nature of the underlying chemical reactions. The distinction between competitive and non-competitive inhibition is important when it becomes necessary to antagonize unwanted drug effects. The newer models are giving more insight into the molecular events occurring in cells with applications in physiology, biochemistry and pharmacology.

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DRUG METABOLISM

G. T. TUCKER

The metabolism or, more accurately, the biotransformation of many drugs is a major determinant of the intensity and duration of their pharmacological and toxic effects. A knowledge of routes and rates of drug metabolism, therefore, is essential to the design of better agents and to the optimal clinical use of existing ones.

Much has been written about this aspect of chemical pharmacology and innumerable texts and reviews have appeared. For comprehensive overviews I recommend Gillette and Mitchell (1975), Parke and Smith (1977) and, particularly for those with a chemical bent, the book by Testa and Jenner (1976a). I shall discuss the subject briefly and with respect to some leading questions.

WHY ARE DRUGS METABOLIZED?

Many drugs are denied substantial exit from the body via the kidney and gastrointestinal tract owing to the possession of lipophilic functional groups (e.g. alkyl, phenyl) that promote reabsorption. A function of drug metabolism, therefore, is to render molecules more polar so that they might be excreted efficiently. In this way metabolism ultimately protects the body against the accumulation and undesirable effects of drugs and of other non-nutrient chemicals (xenobiotics) presented to it from the environment.

Protection is not guaranteed by metabolism, however, as along the way the formation of highly reactive intermediates may be responsible for serious toxicity. Similarly, metabolic products may have greater pharmacological activity than the parent drug (e.g. morphine formed from codeine) or even quite different effects (e.g. isoniazid from iproniazid). Activation of inert compounds by metabolism also occurs. For example, prontosil, one of the first synthetic drugs, is without any antibacterial effect *in vitro*, but in the body is converted to active sulphanilamide. This principle of giving a "pro-drug", that is, an inactive compound which is subsequently metabolized to an active form, is now being exploited deliberately, for instance in the use of esters of chloramphenicol and ampicillin, to improve drug delivery and to reduce side-effects at the site of administration (Digenis and Swintosky, 1975).

HOW ARE DRUGS METABOLIZED?

Routes

In the process of metabolism, drugs undergo "functionalization" and "conjugation" reactions, or both (Testa and Jenner, 1978). The former refers to the introduction, exposure or modification of specific chemical groups and is mediated by oxidation, reduction or hydrolysis. Conjugation involves linkage of the drug itself, or of a primary metabolite produced by a functionalization reaction, with endogenous compounds such as acetate, glycine, sulphate or glucuronic acid. The products usually, but not always, exhibit significantly enhanced water-solubility.

The major pathways and end-products of drug metabolism are indicated in table I, together with substrate examples of particular relevance to the anaesthetist. A number of more esoteric routes have recently been discovered and these have been reviewed by Israili, Dayton and Kiechel (1977) and by Jenner and Testa (1978).

Faced with a chemical structure, it is not too difficult then to make an educated guess as to the likely routes of metabolism. For example, amide-hydrolysis, N-demethylation and aromatic hydroxylation would all be predicted for mepivacaine (fig. 1), and the last two routes have indeed been documented

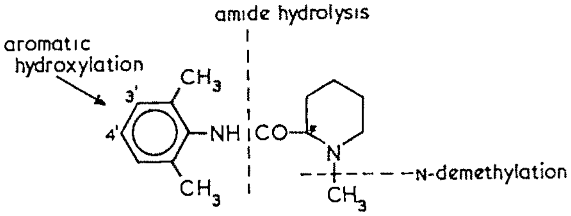

FIG. 1. Mepivacaine—some expected routes of metabolism. (* Denotes an asymmetric carbon atom.)

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TABLE I. *Major routes of drug metabolism*

	Functionalization reactions	
Oxidations		
Aliphatic hydroxylation	$R\cdot CH_2R' \longrightarrow R\cdot CHOH\cdot R'$ (alcohol)	e.g. thiopentone, methohexitone, pentazocine, pethidine, glutethimide, doxapram
Aromatic hydroxylation	$R\cdot C_6H_5 \longrightarrow R\cdot C_6H_4\cdot OH$ (phenol)	e.g. chlorpromazine, lignocaine, bupivacaine, mepivacaine, pethidine, phenobarbitone, glutethimide
O-Dealkylation	$R\cdot O\cdot CH_2R'$ (ether) $\longrightarrow [R\cdot O\cdot CHOH\cdot R'] \longrightarrow R\cdot OH$ (alcohol) $+ R'\cdot CHO$ (aldehyde)	e.g. phenacetin, codeine, methoxyflurane, fluroxene
N-Dealkylation	$R\cdot NHCH_2R'$ (2° amine) $\longrightarrow [R\cdot NHCHOH\cdot R'] \longrightarrow R\cdot NH_2$ (1° amine) $+ R'\cdot CHO$ (aldehyde)	e.g. ephedrine, isoprenaline
	$R_2N\cdot CH.R'$ (3° amin $\longrightarrow [R_2N\cdot CHOH\cdot R'] \longrightarrow R_2NH$ (2° amine) $+ R'\cdot CHO$ (aldehyde)	e.g. lignocaine, mepivacaine, bupivacaine, etidocaine, pethidine, chlorpromazine, pethidine, ketamine, fentanyl, morphine, codeine, atropine, methadone, propoxyphene, diazepam (ring amide)
S-Dealkylation	$R\cdot S\cdot CH_2R'$ (sulphide) $\longrightarrow [R\cdot S\cdot CHOH\cdot R'] \longrightarrow R\cdot SH$ (thiol) $+ R'\cdot CHO$ (aldehyde)	e.g. methitural
N-Oxidation	$R\cdot NH_2$ (1° amine) $\longrightarrow R\cdot NHOH$ (hydroxylamine)	e.g. norpethidine
	$R_3\cdot N$ (3° amine) $\longrightarrow R_3N \rightarrow O$ (amine oxide)	e.g. chlorpromazine, tetracaine, morphine, pethidine
S-Oxidation	$R\cdot S\cdot R'$ (sulphide) $\longrightarrow R\cdot \overset{\overset{O}{\Vert}}{S}\cdot R'$ (sulphoxide)	e.g. chlorpromazine
Deamination (equivalent to N-dealkylation	$R_2CH\cdot NHR'$ (amine) $\longrightarrow [R_2CHOH\cdot NHR']$ (carbinolamine) $\longrightarrow R_2CO$ (aldehyde or ketone) $+ R'\cdot NH_2$ (amine or ammonia) $R_2CH\cdot NHR' \longrightarrow R_2C{=}NOH$ (oxime) $\longrightarrow R_2CO + R'\cdot NH_2$	e.g. amphetamine
Desulphuration	$R\cdot \overset{\overset{S}{\Vert}}{C}\cdot R'$ (thioketone) $\longrightarrow \left[R\cdot \overset{\overset{S\cdot OH}{\Vert}}{C}\cdot R'\right] \longrightarrow R\cdot \overset{\overset{O}{\Vert}}{C}\cdot R'$ (ketone)	e.g. thiobarbiturates
Dehalogenation (X = Cl or Br)	$R\cdot CH(X)_2$ (alkylidene halide) $\longrightarrow \left[R\cdot \overset{\overset{OH}{\vert}}{C}(X)_2\right] \longrightarrow R\cdot COOH$ (carboxylic acid)	e.g. halothane, methoxyflurane, enflurane

TABLE I (*cont.*)

	Functionalization reactions	
Reductions		
Azo reduction	$R\cdot N{=}N\cdot R' \longrightarrow R\cdot NH_2 + R'\cdot NH_2$ (1° amines)	e.g. fazadinium
Nitro reduction	$R\cdot NO_2 \longrightarrow R\cdot NH_2$ (1° amine)	e.g. nitrazepam
Carbonyl reduction	$R\cdot CO\cdot R'$ (ketone) $\longrightarrow R\cdot CHOH\cdot R'$ (alcohol)	e.g. prednisone
Alcohol dehydrogenase	$R\cdot CH_2OH \longrightarrow R\cdot CHO$ (aldehyde)	e.g. ethanol
	$R\cdot CH(OH)_2 \longrightarrow R\cdot CH_2OH$ (alcohol)	e.g. chloral hydrate
Hydrolyses		
Ester hydrolysis	$R\cdot COOR' \longrightarrow R\cdot COOH + R'OH$ (carboxylic acid) (alcohol)	e.g. acetylsalicylic acid, procaine, chloroprocaine, tetracaine, cocaine, suxamethonium, propanidid, pethidine, etomidate, pancuronium*
(* equivalent to deacetylation)		
Amide hydrolysis	$R\cdot CONHR' \longrightarrow R\cdot COOH + R'NH_2$ (carboxylic acid) (amine)	e.g. prilocaine, lignocaine, etidocaine, fentanyl
	Conjugation reactions	
Glucuronide conjugation		
O-Glucuronides	$\left.\begin{array}{l} R\cdot OH \\ \text{(alcohol)} \\ R\cdot C_6H_4OH \\ \text{(phenol)} \end{array}\right\} + \text{UDPGA} \xrightarrow{\text{UDP-glucuronyl-transferase}} \left\{\begin{array}{l} R\cdot O\text{gluc.} \\ R\cdot C_6H_4O\text{gluc.} \end{array}\right. + \text{UDP}$	e.g. oxazepam, paracetamol, morphine, codeine, nalorphine, naloxone
N-Glucuronides	$\left.\begin{array}{l} R\cdot C_6H_4\cdot NH_2 \\ \text{(amine)} \\ R\cdot SO_2NH\cdot R' \\ \text{(sulphonamide)} \end{array}\right\} + \text{UDPGA} \xrightarrow{\text{UDP-glucuronyl-transferase}} \left\{\begin{array}{l} R\cdot C_6H_4NH\text{gluc.} \\ R\cdot SO_2\underset{\text{gluc.}}{\underset{\vert}{N}}R' \end{array}\right. + \text{UDP}$	
Sulphate conjugation	$\left.\begin{array}{l} R\cdot OH \\ \text{(alcohol)} \\ R\cdot C_6H_4OH \\ \text{(phenol)} \end{array}\right\} + \text{PAPS} \xrightarrow{\text{sulphokinase}} \left\{\begin{array}{l} R\cdot OSO_3H \\ R\cdot C_6H_4O\cdot SO_3H \end{array}\right. + \text{ADP}$	e.g. paracetamol, morphine, isoprenaline

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TABLE I (*cont.*)

Conjugation reactions				
Acetylation				
	$R\cdot C_6H_4\cdot NH_2$ (amine)	$\xrightarrow{ATP/Co\text{-}A}$	$R\cdot C_6H_4\cdot NHCOCH_3$	e.g. procaineamide
	$R\cdot SO_2NHR'$ (sulphonamide)		$R\cdot SO_2\cdot \underset{\substack{\vert \\ COCH_3}}{N}R'$	
Methylation				
	$R\cdot C_6H_4OH$ (phenol)	$+\ SAM \xrightarrow{methyltransferase}$	$R\cdot C_6H_4OCH_3$	e.g. morphine
	$R\cdot NH_2$ (amine)		$R\cdot NHCH_3$	e.g. noradrenaline
Conjugation with amino acids				
	$R\cdot C_6H_4\cdot COOH$ (carboxylic acid)	$+\ glycine \longrightarrow$	$R\cdot C_6H_4\cdot CONHCH_2COOH$ (hippuric acid)	e.g. salicylic acid
Conjugation with glutathione				
	$R\cdot C_6H_4$	$+\ GSH \longrightarrow$	$R\cdot C_6H_4\cdot S\cdot CH_2CH(COOH)\cdot NHCOCH_3$ (mercapturic acid)	e.g. paracetamol

Co-Factors: UDPGA = uridine diphosphate glucuronic acid; PAPS = adenosine-3′-phosphate-5′-phosphosulphate; GSH = glutathione; SAM = S-adenosylmethionine; ATP/Co-A = adenosine triphosphate/acetyl coenzyme A.

(Thomas and Meffin, 1972; Meffin, Long and Thomas, 1973; Meffin and Thomas, 1973). Less easy, however, is an estimate of the relative contribution of each pathway to overall transformation. Furthermore, in the case of mepivacaine, one also has to contemplate the possibility that aromatic hydroxylation could be selective for one or other of the 3′- or 4′-positions; that is, regioselective metabolism may occur (Testa and Jenner, 1976b). As it happens, in man, both hydroxy compounds are excreted in the urine but at markedly different rates (Meffin and Thomas, 1973). Notice also that mepivacaine has an asymmetric carbon atom. Therefore, although the racemate is used clinically, metabolism of the component optical isomers may not be the same; the possibility of stereoselective metabolism of drugs becomes a further consideration (Jenner and Testa, 1973).

Mechanisms

Enzymes responsible for oxidation, reduction, hydrolysis and glucuronide formation are embedded in the endoplasmic reticulum of cell membranes and, on ultracentrifugation of sub-cellular components, they can be located in the so-called microsomal fraction.

The microsomal drug oxidation system is particularly versatile and non-specific. Its catalytic components include flavoprotein reductases, phospholipid and haemoproteins, with NADPH and molecular oxygen as co-factors. Cytochrome P-450 serves as a terminal oxidase in a complex chain of events and is directly involved in the binding of drug to the microsomes. It is sensitive to carbon monoxide and when reduced in the presence of this gas exhibits an absorption maximum at 450 nm, hence its name (Omura and Sato, 1964). An NADH-dependent electron transfer system, operating via cytochrome b_5, also appears to be involved and possibly causes the dissociation of the trimolecular complex of reduced cytochrome P-450, oxygen and drug substrate (Estabrook and Cohen, 1969). Thus, one atom of oxygen is incorporated into the substrate and the other is reduced to water. This dual destiny of the two oxygen atoms explains the terms "mixed function oxidase" and "mono-oxygenase" often used to describe the enzyme system (Orrenius, 1971).

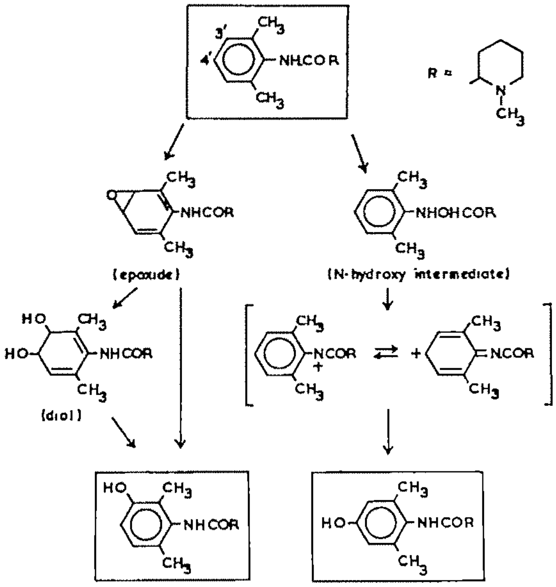
Although the mixed function oxidase system has now been studied for 20 years, there are still many outstanding problems to be solved. These include, for example, the identification of the reactive oxygen species (a superoxide radical perhaps?) (Paine, 1978); an assignment of the role of multiple forms of cytochrome P-450 in relation to substrate specificity (Lu, Kuntzman and Conney, 1976; Warner, La Marca and Neims, 1978); and the elucidation of the spatial organization of the components of the system, with respect not only to each other, but also to nearby reductases and UDP-glucuronyl transferase (Estabrook et al., 1971; Gillette, 1971).

Unlike the enzyme systems already discussed, those responsible for the remaining conjugation reactions are located primarily in the cytosol and, in the case of acetylation, also in the mitochondria.

Between the attachment of a drug molecule to the various enzymes and the formation of the end-products indicated in table I, several complex chemical rearrangements occur. Mechanisms involving the formation of quite different intermediates may even exist for ostensibly the same overall type of product. To use mepivacaine as an example again, its 3′-hydroxy metabolite seems to arise from an epoxide intermediate, while the 4′-hydroxy isomer is probably generated via rearrangement of an N-hydroxy derivative (Meffin and Thomas, 1973) (fig. 2).

WHERE ARE DRUGS METABOLIZED?

In keeping with the strategic position of the liver between the port of entry of many chemicals—namely the gastrointestinal tract—and the rest of the body, this organ is the most active with respect to drug metabolism (Remmer, 1970). Following oral administration of many drugs, extensive "first-pass" metabolism in the liver, after their uptake into the hepatic portal vein, significantly reduces their systemic availability. This phenomenon explains, for example, why 100 mg of oral pethidine is pharmacologically equivalent to 50 mg given by i.m. injection, since the hepatic extraction ratio of the drug is about 0.5 (Mather and Tucker, 1976). Understanding of the mechanism of the hepatic first-pass effect is incomplete, but it appears to involve rapid and sustained binding of unchanged drug to cytochrome P-450 followed by subsequent rate-limiting biotransformation (Grundin et al., 1974; McEwan, Shand and Wilkinson, 1974; Von Bahr et al., 1976). This avid microsomal binding of drugs with high first-pass extraction may serve to protect the delicate biochemical machinery of the mitochondria from deleterious effects that the drugs might otherwise produce (Grundin, Thor and Orrenius, 1975). In general, current knowledge of relationships between



RAT	60%	0%
HUMAN		
adult	16%	11%
neonate	<2%	<2%

FIG. 2. Postulated routes of formation of 3'- and 4'-hydroxy mepivacaine and their urinary recoveries (free + conjugated) (Thomas and Meffin, 1972; Meffin and Thomas, 1973; Moore et al., 1978).

drug metabolism and intermediary metabolism is minimal, particularly with regard to the sharing of available energy (Moldéus et al., 1974).

Enzymes within the gut wall also contribute to first-pass loss after oral administration of some drugs. For example, gastrointestinal esterases convert about 30% of a dose of aspirin to salicylic acid in the dog (Harris and Riegelman, 1969) and chlorpromazine is extensively conjugated with sulphate in the rat intestine (Curry, D'Mello and Mould, 1971). N-demethylation of flurazepam by human small intestine has also been documented (Mahon, Inaba and Stone, 1977).

Metabolism in the intestinal lumen, of drugs and their metabolites secreted via the bile tends to reverse the effects of hepatic microsomal enzymes. Compounds are often rendered less polar and, therefore, available for reabsorption leading to the establishment of enterohepatic recycling. For example, the glucuronides of morphine and etorphine are hydrolysed back to the parent drugs, which may then contribute to further activity after reabsorption (Plaa, 1975). Bacterial enzymes play a significant role in this process (Scheline, 1973). Also, the anaerobic environment in which they exist encourages reductive reactions, which again tend to offset the largely oxidative changes wrought by the liver. The nitro group of nitrazepam, for example, is susceptible to attack by bacterial reductases, as indicated by impaired metabolism of this drug in germ-free rats (Hewick and Shaw, 1978).

Several of the agents commonly injected by the anaesthetist are rapidly metabolized by blood-borne enzymes. Suxamethonium (Holst-Larsen, 1976), propanidid (Doenicke et al., 1968), cocaine (Stewart et al., 1977), procaine and other related local anaesthetics (Foldes et al., 1965) are substrates, in man, of both plasma pseudocholinesterase and hepatic esterases, although ester hydrolysis of other agents, such as pethidine (Mather and Meffin, 1978), etomidate (Ghoneim and Korttila, 1977) and pancuronium (Buzello, 1975) may be confined to the liver.

The lung is a major excretory organ for some compounds, notably the inhalation anaesthetics. However, it also has a capacity for drug metabolism, although this is less marked than that of the liver (Hook and Bend, 1976). Furthermore, if metabolism does occur it may be considerably less when a drug reaches the lung via the circulation than when it enters from the alveoli. This is true in the case of O-methylation of isoprenaline (Briant et al., 1973); whether it also applies to substrates of the pulmonary mixed function oxidase system is less clear. Pulmonary metabolism of prilocaine has been demonstrated in animals (Akerman et al., 1966) and it may also contribute to the elimination of the local anaesthetic in man, since its total clearance was found to exceed the sum of its renal clearance plus hepatic blood flow (Arthur et al., 1979).

Although microsomal drug-metabolizing enzymes and cytochrome P-450 have been found in the placenta, the ability of this structure to transform the majority of drugs appears negligible in contrast to the liver (Chakraborty, Hopkins and Parke, 1972; Juschau, 1976). This is consistent with a view of the placenta as a fetal excretory organ, since a role in rendering drugs more polar would tend to be counterproductive in this respect. Any increase in water solubility would hinder rapid diffusion of molecules across the lipid membranes of the placenta back to the mother.

HOW TOXIC ARE DRUG METABOLITES?

Toxicity resulting from the formation of drug metabolites is generally manifest in one of two ways. First, it can arise from the dose-related accumulation of metabolites normally readily excreted or without overt effect. This type of toxicity is usually predictable and examples of anaesthetic interest include methaemoglobinaemia as a result of the action of oxidized forms of o-toluidine produced from high doses of prilocaine (Hjelm and Holmdahl, 1965) and nephrotoxicity caused by the accumulation of inorganic fluoride ion following administration of methoxyflurane (Mazze, Cousins and Kosek, 1972). More recently, there has been concern that excessive amounts of bromide ion formed from halothane might contribute to postoperative sedation and psychological alterations in surgical patients (Johnston et al., 1975; Tinkler, Gandolfi and Van Dyke, 1976). The anaesthetist may also be at risk in this respect from chronic exposure to low concentrations of halothane vapour in the operating theatre (Duvaldestin, 1977).

The second type of toxicity is more insidious and less predictable and follows the metabolic activation of chemically stable drugs to potent alkylating and arylating intermediates that can form covalent bonds with tissue macromolecules. Epoxides, N-hydroxy derivatives and nitrosamines are particularly implicated in these reactions, which may result in cell necrosis, carcinogenesis, teratogenesis, mutagenesis, blood dyscrasias and hypersensitivity phenomena (Parke, 1974). In an anaesthetic context there is strong, although not yet conclusive, evidence that rare, but often fatal, cases of liver damage after exposure to some halocarbon inhalation agents are related to the formation of reactive intermediates during their metabolism (Van Dyke, 1972; Brown and Sipes, 1977; Cohen, 1978). The occasional allergic reaction to procaine and other local anaesthetics of the ester type is probably associated with linkage between a reactive derivative of their para-amino benzoic acid moiety and a protein (Covino and Vassallo, 1976).

HOW VARIABLE IS DRUG METABOLISM?

Even when disease is not included as a factor, drug metabolism varies widely as a complex function of genetic and environmental influences, species, strain and age. Gender is a significant variable in some animals, but less so in humans (Giudicelli and Tillement, 1977).

Species variation

This aspect is, of course, the particular headache of pharmacologists and toxicologists seeking the best animal models for the pre-clinical testing of new drugs. Both quantitative and qualitative differences exist in the ways in which different animals metabolize drugs, yet again a point which can be illustrated with mepivacaine. Total urinary excretion of the conjugated hydroxy products of this agent amounts to 60% of the dose in the rat, compared with only 25% in man and, whereas in the latter the recovery is comprised of equal quantities of the 3′- and 4′-hydroxy isomers, the rat only excretes, and presumably therefore only forms, the 3′-hydroxy product (Thomas and Meffin, 1972) (fig. 2).

Atropine and fluroxene are good examples of agents showing dramatic species differences in activity closely related to variability in drug metabolism. An "atropinesterase" accounts for a rapid disappearance of atropine from the plasma of some strains of rabbits, but it is completely absent from human plasma (Williams, 1959). Fluroxene enjoyed more than a decade of uneventful clinical use before it was discovered to be invariably lethal to no less than four animal species (mouse, cat, rabbit and dog) after only one to three exposures. Although the mechanism of this difference has not been established for sure, it appears to relate to the formation, by common laboratory animals but not man, of substantial quantities of the toxic metabolite trifluoroethanol (Cascorbi and Singh-Amarananth, 1972; Johnston et al., 1973). As pointed out by Wardell (1973), fluroxene is an example of a useful compound that would not have passed today's more stringent pre-clinical screens. However, perhaps it is fortunate that it is no longer available in view of the additional finding that, unlike other inhalation agents, it has a mutagenic effect on bacteria cultured in the presence of human or rat liver microsomes (Baden et al., 1976). Even so, a question still remains as to whether bacteria are any better than animals in predicting drug toxicity in humans? Should more emphasis be placed on post-marketing surveillance of new drugs?

Individual variation

At this level, most clinicians begin to take more of an interest in the variability of drug metabolism. Again, differences may be manifest both in the overall rate of transformation and in the composition of metabolic products.

Within groups of young, healthy subjects the coefficients of variation of the urinary excretion of ring-hydroxy products of mepivacaine and of its total metabolic clearance were found to be 20% and 40%, respectively (Tucker and Mather, 1975; Moore et al., 1978). These figures are representative of those reported for several other drugs (Alvan, 1978), although in some cases, such as phenytoin and salicylate, the variance is further accentuated by saturation of metabolizing enzymes in the therapeutic range of plasma drug concentrations. There is no evidence, as yet, that variability in hepatic clearance of highly extracted drugs is any greater or less than that of lowly extracted compounds (Alvan, 1978). Systemic clearance of the former will be largely determined by liver blood flow, while that of the latter will more closely reflect the intrinsic ability of metabolic enzymes to remove drug (Wilkinson and Shand, 1975).

The rate and manner in which an individual metabolizes drugs is partly determined by his or her inheritance (Smith and Rawlins, 1973). Polymorphism exists in the enzymes catalysing some routes of biotransformation, allowing the recognition of different phenotypes. Hence, whether one is a "good" or a "poor" metabolizer of the substrates involved can significantly influence the degree of drug response and the probability of side-effects. The rare individual with atypical pseudocholinesterase who responds abnormally to suxamethonium and procaine exemplifies this phenomenon (Harris, 1964). Acetylation of several compounds, including for example the amine metabolite of nitrazepam (Karim and Price-Evans, 1976), and alicyclic hydroxylation of debrisoquine (Mahgoub et al., 1977; Tucker et al., 1977a) have also been shown to exhibit polymorphism. In contrast, the metabolism of most drugs is under polygenic control, a large number of genes influencing individual deviation in a normally distributed population. Under these circumstances, the contribution of heredity to variability is best demonstrated by studies with twins. Accordingly, the metabolism of halothane and the plasma elimination $T_{\frac{1}{2}}$ of other agents show close agreement in identical but not in fraternal pairs (Cascorbi et al., 1971; Vesell, 1974).

Potential environmental influences accounting for individual variation in drug metabolism are legion (Alvares, 1978) and include selective effects of diet (Krishnaswamy, 1978), cigarette and marijuana smoking (Jusko, 1978; Jusko et al., 1978) and the consumption of alcohol (Sellers and Holloway, 1978). Enzyme induction (Dollery, 1972) is more common than enzyme inhibition and an interesting study by Keeri-Szanto and Pomeroy (1971) graphically illustrates its potential importance. Thus, significant correlations between high maintenance dosage requirements of pentazocine and urban living as well as smoking were found which were tentatively assigned to enzyme induction caused by ambient or self-inflicted atmospheric pollution. Subsequently, Vaughan, Beckett and Robbie (1976) confirmed that smokers metabolize 40% more of the drug than non-smokers. Smoking has also been associated with reduced efficacy and fewer side-effects of several other therapeutic agents (Miller, 1977).

Concern over toxic effects of drugs in patients at the extreme ends of the age range has prompted increasing interest in drug metabolism in neonates (Morselli, 1976), children (Rane and Wilson, 1976) and in the elderly (Crooks, O'Malley and Stevenson, 1976).

Although generalizations are difficult, there is good evidence that some, but not all, of the routes of drug transformation are deficient in the newborn. This is particularly true of hydroxylating activity. Mepivacaine, for example, is hardly converted to ring-hydroxy metabolites (fig. 2), a deficiency which contributes to a plasma drug clearance in neonates of less than half of the adult value (Moore et al., 1978). In turn, the accompanying prolongation of elimination $T_{\frac{1}{2}}$ may help to explain temporary neurobehavioural deficits found in babies delivered from mothers receiving extradural injections of this agent (Scanlon et al., 1974).

There is some support for the proposal that hepatic metabolism of drugs may also be impaired in advanced age. This appears to be so for pethidine and amylobarbitone, for example (Irvine et al., 1974; Chan et al., 1975; Mather and Meffin, 1978). However, although other drugs, including lignocaine, exhibit prolonged elimination $T_{\frac{1}{2}}$ in geriatric patients, this is related to changes in distribution rather than in metabolism (Nation, Triggs and Selig, 1977). It is increasingly clear that apparent effects of old age on drug metabolism in man may be more a function of age differences in other factors, such as diet and smoking, rather than of age *per se* (Vestal, 1978). Decline in liver size as well as in enzyme activity may also be important (Swift et al., 1978).

Circadian variation in drug metabolizing enzyme activity has been documented in animals (Tredger and Chhabra, 1977), but evidence for this phenomenon in man is less convincing. For example, although the elimination $T_{\frac{1}{2}}$ of phenacetin and paracetamol were found to be 15% shorter at 2 p.m. than at 6 a.m., the differences were largely the result of distributional changes (Shively and Vesell, 1975).

CAN DRUG METABOLISM BE PREDICTED?

Despite the fact that drug metabolism is so variable, some limited success has been achieved in predicting overall rates. These predictions have taken several forms.

Same drug and species—in vitro *to* in vivo

Reasonable estimates of the clearance of various drugs in intact rats and in the isolated perfused rat liver have been made from $V_{\max}$ and K_m values determined independently by microsomal enzyme assays (Dedrick, 1973; Rane, Wilkinson and Shand, 1977; Collins, Blake and Egner, 1978; Lin et al., 1978).

Same drug—species to species

Transforming a mouse into a man in pharmacokinetics is relatively easy when drug clearance is primarily sensitive to changes in perfusion rate rather than metabolism. This may be done by correcting dose for body weight and real time for circulation time (Dedrick, 1973). Inter-species conversion is much more difficult when metabolism is rate-limiting, although Walker (1978) has found a good correlation between microsomal monooxygenase activity and body weight in a range of mammals.

Same species—drug to drug

If quantitative correlations can be shown between physicochemical properties and biotransformation in a series of structurally related compounds, it ought to be possible to predict the fate of a new homologue or analogue. Comprehensive studies with barbiturates illustrate this principle and indicate a prominent role of lipophilicity, although some structural features are also important (Tong and Lien, 1976; Testa, 1978). Variability in hepatic clearance of the clinically used amide-type local anaesthetic agents in man appears related to structural differences rather than to lipid solubility. In mepivacaine and bupivacaine the amino group is incorporated into a ring and these compounds exhibit lower clearances than lignocaine and etidocaine, in which the amino group is in an alkyl chain (Tucker, 1975).

Same individual—drug to drug

Having adjusted the dosage of one drug in a patient, selection of the right doses of other drugs would be considerably easier if relationships existed between the metabolic fate of different agents in the same individual. This possibility has been investigated by several groups who have reported encouraging correlations amongst a variety of drug substrates (Vesell and Page, 1968; Hammer, Mårtens and Sjöqvist, 1969; Davies and Thorgeirsson, 1971; Kadar et al., 1973; Boobis et al., 1979). Also of significance in this context is the recent finding that polymorphism in the alicyclic hydroxylation of debrisoquine is common to N-dealkylation of phenacetin and aromatic hydroxylation of guanoxan (Sloan et al., 1978). However, antipyrine clearance, which is correlated with the production of its 4-hydroxy metabolite (Vesell et al., 1975; Boobis et al., 1979), did not show a relationship with debrisoquine hydroxylator status (Tucker et al., 1977a). This could reflect differences in the activity of multiple forms of cytochrome P-450, a potential complicating factor in the typing of individuals for their ability to metabolize drugs.

HOW DO PATHOPHYSIOLOGICAL CHANGES AFFECT DRUG METABOLISM?

When assessing the influence of surgery, pregnancy and disease on drug metabolism it is particularly important to distinguish effects on the activity of drug metabolizing enzymes *per se* from those on the delivery of drug to the enzymes. In this respect, drugs tend to gravitate to one of two classes (Wilkinson and Shand, 1975; Blaschke, 1977). There are those with high hepatic extraction ratios (>0.5), the systemic clearances of which are sensitive to hepatic blood flow rather than hepatic enzyme activity and the elimination of which is a function of total (free plus bound) blood drug concentration. Examples of these "flow-limited drugs" include lignocaine, propranolol and pethidine. In contrast, "capacity-limited drugs", which include antipyrine, phenytoin, theophylline and diazepam, are characterized by a low hepatic extraction ratio (<0.2), a systemic clearance sensitive to hepatic function rather than flow, and a rate of elimination proportional to unbound drug concentration.

Surgery

Pessayre and colleagues (1978) measured antipyrine clearances before and after operation in patients undergoing surgery with general anaesthesia and found that short procedures were followed by increased activity of hepatic drug-metabolizing enzymes, whereas protracted operations were followed by decreased activity (fig. 3). They suggested that the former effect may be a consequence of enzyme-induction by drugs used for premedication and anaesthesia (see below), whereas the latter effect may be the result of major surgical trauma. Surgery is often associated with a number of factors known to depress drug-metabolizing activity, for example inflammation (Whitehouse and Beck, 1973), fever (Elin, Vesell and Wolff, 1975; Trenholme et al., 1976) and nitrogen-free infusions (Alvares et al., 1976). Bed rest after operation tends to increase drug clearance and this may contribute to findings after short operations (Elfström and Lindgren, 1978). The clearance of flow-dependent drugs should be particularly sensitive to recumbency since there is a 20–50% increase in hepatic blood flow compared with the erect position (Culbertson et al., 1951). On the other hand, the clearance of these compounds is also more likely to be depressed by any reduction in hepatic perfusion associated with hypoxia after operation (Roth and Rubin, 1976).

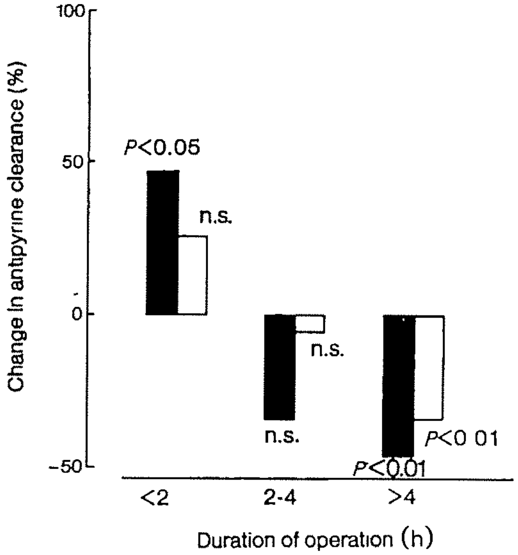


FIG. 3. Changes in antipyrine clearance in three groups of patients operated upon for 2 h or less, 2–4 h and more than 4 h, respectively. ■ = 3 days after surgery; □ = 6 days after surgery. (From Pessayre et al., 1978, with permission.)

Pregnancy

Although longitudinal studies have not been done, data for pethidine (Morgan et al., 1978) and etidocaine (Morgan et al., 1977) suggest no differences in the total clearance of flow-limited drugs in pregnant women at term compared with control surgical patients. The same is true for diazepam, although post-natal distributional changes are apparent (Moore and McBride, 1978). Biotransformation of phenytoin and of other anticonvulsants increases markedly during pregnancy but decreases again at the puerperium (Eadie, Lander and Tyrer, 1977).

Disease

The application of pharmacokinetic analysis over the past 5 years has done much to advance our limited understanding of the mechanisms of altered drug handling in many disease states (Benet, 1976). Space allows mention of only selected conditions of particular interest to the anaesthetist.

In heart failure, the metabolic clearance of both lignocaine and theophylline is significantly impaired, indicating that changes in both hepatic blood flow and function render it necessary to reduce drug dosage (Benowitz and Meister, 1976).

Relatively few studies designed to assess drug disposition in patients with respiratory disease have been reported (Du Souich et al., 1978). However, available evidence suggests that, unlike acute hypoxia, chronic hypoxia may be accompanied by enhanced activity of some drug metabolizing enzymes (Agnihotri et al., 1978). Also, an association between rapid clearance of antipyrine and lung cancer has been found by Ambre and colleagues (1977), although this has not been confirmed by others (Tschantz et al., 1977).

Whereas hydrolysis and some acetylation reactions are slowed in patients with renal failure, conjugation is generally normal and oxidation may even be accelerated (Reidenberg, 1977). Being relatively polar, drug metabolites tend to accumulate during kidney disease and in some instances this may precipitate adverse effects (Drayer, 1976). For example, norpethidine, formed from pethidine, and hydroxyamylobarbitone, from amylobarbitone, contribute to excessive central excitatory and depressant effects, respectively, in patients with renal failure (Balasubramaniam et al., 1972; Szeto et al., 1977).

Although the liver is the main site of drug metabolism, the effect of liver disease on drug disposition is not always consistent or predictable (Wilkinson and Schenker, 1975; Branch and Shand, 1976; Rowland et al., 1976; Blaschke, 1977). An understanding of the role of impaired drug metabolism is particularly relevant to the avoidance of hepatic coma when patients with liver disease require sedation. In this context, and on the basis of some selectivity in the impairment of different routes of metabolism in liver disease, oxazepam and lorazepam would appear to be more suitable sedatives than diazepam or chlordiazepoxide (Hoyumpa, 1978) (fig. 4). However, the possibility of different cerebral sensitivity to each of these benzodiazepines remains to be investigated. Most data on the influence of liver disease on drug metabolism have been collected in patients with cirrhosis or hepatitis, whereas relatively little work has been done in connection with obstructive jaundice (Carulli et al., 1975).

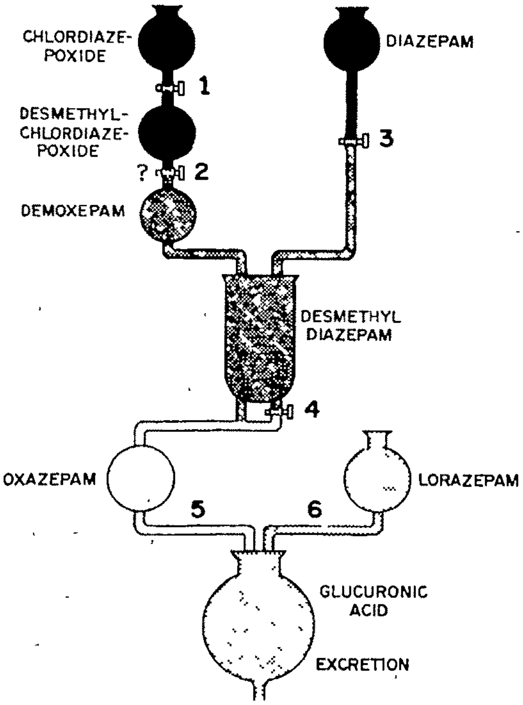


FIG. 4. Schematic representation of benzodiazepine metabolism and the probable or presumed steps (numbered) which are impaired in the presence of liver disease as indicated by the stopcocks. Decreased metabolism of the compound is indicated by "closing off" of the stopcock and the lighter shading of the metabolite, representing decreased metabolite formation at this step. As seen in this simplistic scheme, metabolism involving the mono-oxygenase system (1–4) appears more readily impaired in liver disease (i.e. chlordiazepoxide and diazepam) than the conjugation pathway (i.e. oxazepam and lorazepam). Note that not all the metabolites of these drugs or metabolic steps are represented in this scheme. 1 = demethylation; 2 = oxidative deamination; 3 = demethylation; 4 = hydroxylation; 5 and 6 = conjugation with glucuronic acid. (From Hoyumpa, 1978, with permission.)

Porphyria is also associated with a selective impairment of some routes of drug metabolism. It may be significant that one of those affected is hydroxylation, a pathway common to many of the drugs that precipitate acute attacks of the condition (Song, Bonkowsky and Tschudy, 1974).

WHICH DRUGS INTERFERE WITH DRUG METABOLISM?

When two or more drugs are administered simultaneously they may at first interact with microsomal enzymes leading to inhibition of metabolism. Subsequently, this may give way after a few hours to an inductive phase, as stimulation of the *de novo* synthesis of enzyme protein, possibly accompanied by an increase in hepatic blood flow, accelerates drug metabolism.

Halothane exhibits this dual effect of inhibition and induction. Although the mechanism is not known, it has been shown to impair the metabolism of phenytoin (Karlin and Kutt, 1970) and warfarin (Ghoneim et al., 1975) in man and of ketamine in the rat (White, Johnstone and Pudwill, 1975). Chronic, but not acute, exposure in animals leads to an increase in the activity of microsomal enzymes, but unaccompanied by increased concentrations of cytochrome P-450 (Rietbrock, Lazarus and Otterbein, 1972; Hallén and Johansson, 1975). Extrapolation of these findings to man is difficult. Daily exposure of operating room staff to trace amounts of halothane appears not to be associated with any increase in antipyrine clearance (Wood, O'Malley and Stevenson, 1974), although the urinary recovery of halothane metabolites may be increased (Cascorbi, Blake and Helrich, 1970). Therefore, self-induction of halothane metabolism, resulting in enhanced formation of reactive intermediates, might promote the likelihood of liver damage, teratogenicity and cancer (Cohen, 1978). Ketamine is another agent that is capable of inducing its own metabolism and this may account for clinical reports of tolerance after repeated doses (Marietta et al., 1976; Livingstone and Waterman, 1978). Diazepam is even more complex since there are suggestions that it both increases (Kanto et al., 1974) and inhibits (Klotz, Antonin and Bieck, 1976) its own metabolism. The latter effect is possibly mediated via product-inhibition resulting from accumulation of N-desmethyl diazepam during chronic dosage. Therapeutic agents which are especially potent enzyme inducers include anticonvulsants and rifampicin (Burley, 1977; Richens, 1977). Therefore, in patients treated with this type of compound, dosage of other drugs may have to be increased to maintain therapeutic effects. On the other hand, if drug metabolites are more active than the parent compound a reduction in dosage could be indicated. Increased production of toxic norpethidine from pethidine in a patient also receiving phenobarbitone illustrates the latter possibility (Stambaugh et al., 1977).

Apart from direct effects on metabolizing enzymes, alterations in the rate of drug metabolism may also be produced by drugs that indirectly or directly influence hepatic blood flow. For example, lignocaine clearance is decreased and increased, respectively, by the haemodynamic effects of propranolol (Branch et al., 1973) and ephedrine (Wiklund, Tucker and Engberg, 1977). Furthermore, by increasing liver blood flow themselves, lignocaine and other local anaesthetics may increase their own clearance (Tucker et al., 1977b). The depressant effects of halothane and other inhalation agents on the circulation may also contribute to their inhibitory effects on drug metabolism (Burney and DiFazio, 1976). Surprisingly, sodium nitroprusside in hypotensive doses did not alter lignocaine clearance in anaesthetized dogs (Shiroff et al., 1977). This suggests that systemic vasodilatation in combination with normal cardiac output does not affect hepatic blood flow.

Cholinesterases are involved in several drug interactions of significance to the anaesthetist. In relation to acetylcholinesterase such interactions may be intended, as in the use of neostigmine to reverse the effects of curare. However, unrecognized inhibition of plasma pseudocholinesterase by anticholinesterases and other drugs may lead to problems. Substrate competition between propanidid and suxamethonium has been demonstrated in man (Doenicke et al., 1968) and clinically relevant concentrations of bupivacaine and etidocaine have been shown to reduce the rate of *in vitro* hydrolysis of chloroprocaine by 10–40% (Lalka et al., 1978). Although some reports have suggested that ketamine prolongs the action of suxamethonium, in this case an inhibitory effect on human plasma pseudocholinesterase is only evident at concentrations greater than those encountered clinically (Schuh, 1975).

CONCLUSIONS

Being specialists in acute medicine, most anaesthetists can cope with the immediate physiological consequences of a patient receiving the wrong dose of a drug. However, on the basis that prevention is better than cure, an understanding of factors affecting the rate of drug metabolism is an essential ingredient of good practice. Adverse biochemical consequences of the use of drugs are more difficult to rectify and, although the anaesthetist should not be unduly worried about most of the multitude of drug metabolites excreted in the patient's urine (let alone in his or her own) after a typical anaesthetic procedure, it is the intermediate products which do not reach the urine that are perhaps of more concern.

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RECENT MOLECULAR THEORIES OF GENERAL ANAESTHESIA

B. Wardley-Smith and M. J. Halsey

The mechanism of anaesthesia has attracted the interest of many eminent scientists. For example, the references in this limited review include such well-known names as Professors Burgen, Eyring, Paton and Pauling, who have all made contributions to different aspects of this field. In view of the wide range of scientific disciplines involved, it is not surprising that, since the introduction of general anaesthesia for surgery in the 1840's, there have been numerous ideas about the mechanisms of action of anaesthetics. By 1900 more than 25 of these had been published, and by the early 1960's more than 100 different theories of the mechanism of narcosis had been proposed. Of these theories, only a few are currently accepted, and this article is intended to discuss the molecular developments in anaesthesia research since the early 1970's.

At first sight much of this work, which involves various model systems, is not directly relevant to the *in vivo* mechanisms of anaesthesia. A complete description of the mechanisms must include an understanding of how anaesthetics affect the integrated nervous system, single neurons and synapses as well as the molecular interactions. These approaches are not entirely separate. For example, the recognition that anaesthetics acted at hydrophobic sites reduced the possibility that anaesthetic actions in aqueous areas of neurons were critical. Anaesthetic research has tended to parallel the developments in human biology, and thus one of the intensive areas of current research is concerned with molecular biology and membrane biophysics. However, it is desirable to review briefly some of the earlier ideas which were important in the formation of the currently fashionable theories.

CORRELATIONS WITH PHYSICAL PROPERTIES

Although almost all the early physical theories of anaesthesia involved lipid solubility, two independent workers (Miller, 1961; Pauling, 1961) proposed an aqueous site of action in the central nervous system. Though different in detail, both theories attempted to relate anaesthetic potency to the stability of the gas hydrate in aqueous solution. Their original correlations for a limited range of agents were reasonable, but studies with more anaesthetics proved that the agreement between potency and hydrate dissociation pressure was much worse than that for potency and oil/gas partition coefficient. These theories of an aqueous site of action have now been mainly abandoned.

It is more generally assumed that anaesthetics act by interaction with a hydrophobic phase somewhere in the nervous system. This idea is not new, however, since one of the best correlations with potency is the solubility of the anaesthetic in olive oil. This was first recognized by H. H. Meyer and by Overton, both in 1901, and the lipid solubility theory that they proposed has been expressed in modern form by K. H. Meyer in 1937, who said that "Narcosis commences when any chemically indifferent substance has attained a certain molar concentration in the lipids of the cell. This concentration depends on the nature of the animal or cell but is independent of the narcotic."

The idea that a physical property of an anaesthetic was critical was further expanded by Ferguson (1939), who found a reasonable correlation between vapour pressure at 37 °C and anaesthetic potency of a series of homologous alcohols. He concluded that thermodynamic activities were important as a measure of anaesthetic potency.

Mullins (1954) carried out a thermodynamic analysis of the data then available to him and suggested that anaesthetic activity was not dependent on solubility alone but also on the molar volume of the anaesthetic. He suggested that anaesthetics might "depress cell function by preventing the passage across cell membranes of any particular molecule or ion, depending only on the degree of volume occlusion occasioned by the narcotic". This was an attractive model, but inclusion of molecular size in the data analysis does not improve the Meyer–Overton correlation between potency and oil solubility. The theoretical thermodynamic approach to anaesthetic

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mechanisms is still in use today. Eyring, Woodbury and D'Arrigo (1973) proposed a molecular mechanism of anaesthesia based on thermodynamic considerations, later expanding their ideas to formulate the lipoprotein conformational change theory (Woodbury, D'Arrigo and Eyring, 1975). In 1974, Hill analysed the results of dissolving anaesthetics in membranes in terms of the "Gibbs free energy hypothesis".

The correlation of physical properties of anaesthetics with anaesthetic potency is still an accepted approach to the subject. In 1969 Eger and his colleagues measured anaesthetic potency in terms of dog MAC and correlated this with both lipid solubility and hydrate dissociation pressure. Three years later Miller and colleagues (1972) correlated anaesthetic potency measured in mice with anaesthetic solubility in solvents of different solubility parameters. In a recent study Franks and Lieb (1978) measured the partition coefficient for 22 anaesthetics in several different solvents, and found that the potency/partition coefficient correlation was better for octanol than for oil, and concluded that the site of action had both polar and apolar characteristics. This concept has been developed quantitatively by Hansch and his colleagues (1975) over the past 8 years.

However, there is a limit to how much information can be obtained from simple solubility characteristics and thermodynamic analysis of whole animal data. It is necessary to look at other physical changes at the molecular level. There have been two main developments, first whole animal pressure reversal studies, and second, the use of model systems of lipids and proteins.

HIGH PRESSURE STUDIES

It is one of the most striking features of anaesthetics that many of their effects are opposed by high hydrostatic or gaseous pressures. This was first demonstrated by Johnson, Brown and Marsland (1942a, b) who showed that the light from luminous bacteria, dimmed by anaesthetics, could be restored by high pressures. Johnson and Flagler (1950, 1951) anaesthetized tadpoles with alcohol until swimming had ceased, and then applied high hydrostatic pressure until swimming had spontaneously started again. Tadpoles were used recently to show that pressure reversal occurred with a far wider range of compounds than had been expected, including narcotics and tranquillizers as well as conventional anaesthetics (Halsey and Wardley-Smith, 1975).

It was not until the early 1970's that a unifying theory was put forward to explain the interactions of anaesthetics and pressure, and to provide a hypothesis of the physical mechanism of narcosis. The critical volume hypothesis (Lever et al., 1971; Miller et al., 1973) was proposed as an extension of the work of Mullins, and states that "anaesthesia occurs when the volume of a hydrophobic region is caused to expand beyond a critical amount by the absorption of molecules of an inert substance. If the volume of this hydrophobic region can be restored by changes of temperature or pressure then the anaesthesia will be removed." This hypothesis assumed that all anaesthetics acted at the same molecular site. It was formulated from experiments using newts. On plotting increases in anaesthetic potency against total pressure for four anaesthetics, a straight line was obtained (fig. 1). This was in accordance with the predictions of the hypothesis, which stated that since equi-narcotic doses of all anaesthetics caused an equal volume increase, the degree of pressure reversal for a given total pressure should be the same for all anaesthetics.

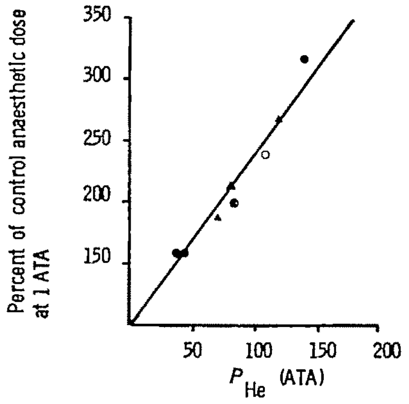

FIG. 1. Original pressure reversal data in newts. x axis—Helium total pressure (P_{He}) in atmospheres absolute (ATA); y axis—percentage of control anaesthetic dose at 1 ATA required to reduce the rolling response of newts to 50% of control value. ● = Nitrogen; ▲ = sulphur hexafluoride; ⊙ = nitrous oxide; △ = carbon tetrafluoride (data from Miller et al., 1973).

The critical volume hypothesis also suggested that "temperature reversal" would occur in a manner similar to pressure reversal, and it was calculated that the effects of a normal anaesthetic dose would be removed on cooling by 10 °C. This effect was predicted on the simple basis that the expansion caused by the anaesthetic could be counteracted by the contraction resulting from cooling. However, this is a more difficult concept to test, as even in cold blooded animals the predominating effect of cooling is hypothermia. Since extreme cases of hypothermia are seen as a state resembling anaesthesia, assessment of anaesthetic potency becomes unreliable.

Spyropoulos (1957) removed the effect of a 3% ethanol solution on the action potential of toad nerve fibre by cooling by 15 °C, but a reduction in solubility would also occur with lowering of temperature, and thus precise analysis of his results is not easy. Preliminary experiments with nitrous oxide and nitrogen on intact animals (Halsey and Higgs, 1976) and with some of the alcohols on an *in vitro* nerve preparation (Richards et al., 1978) showed no evidence of "temperature reversal of anaesthesia". However, because of difficulties of interpretation this aspect of the critical volume hypothesis remains one that is not resolved.

Early experiments in normothermic mammals (Halsey and Eger, 1971) provided support for the hypothesis since the pressure reversal values coincided with the predicted straight line. Subsequent mammalian experiments, however, produced less clear cut results. Smith and colleagues (1975) studied the pressure reversal of argon and nitrogen anaesthesia, while Kent and colleagues (1977) expanded the range of agents to include the volatile clinical anaesthetic, isoflurane. The original work with nitrous oxide was extended to greater pressures (White and Halsey, 1974). Recently Miller, Wilson and Smith (1978) have studied the perfluorinated anaesthetics. Examples of all these data are plotted in figure 2.

The first quantitative experiments with non-gaseous anaesthetics in mammals were by Winter and colleagues (1976). They used phenobarbitone in mice, and gave a single dose before compression. The anaesthetic effect of this agent was reversed by pressure, and the increase in ED_{50} at 103 atm was equal to that for isoflurane, but greater than that for nitrous oxide. However, the technique of pre-administration of a single dose before compression makes it hard to be certain that changes in metabolism are not taking place, especially with long-acting anaesthetics such as phenobarbitone.

We have developed a continuous infusion technique for studying the short acting i.v. anaesthetics at pressure. Initial experiments, with Althesin (Bailey et al., 1977), have been extended to other i.v. anaesthetics (Halsey, Wardley-Smith and Green, 1978). The degree of pressure reversal varied considerably between the different agents. Miller and Wilson (1978) compared the non-gaseous agents ethyl carbamate, α-chloralose and phenobarbitone, with argon and nitrogen and found differing degrees of pressure reversal between the two groups, but agreement within them. Some examples of the pressure reversal data for the i.v. agents are shown in figure 3.

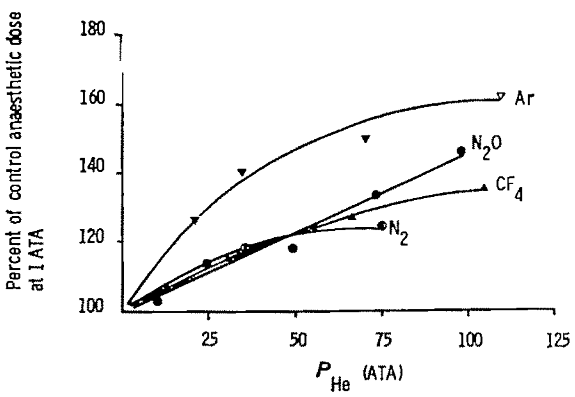

FIG. 2. Representative examples of data for pressure reversal of gaseous anaesthetics in mice. *x* axis—As figure 1; *y* axis—percentage of control anaesthetic dose at 1 ATA required to reduce righting reflex of mice to 50% of control value. ∇ = Argon (Ar) (Smith et al., 1975); ● = nitrous oxide (N_2O) (White and Halsey, 1974); ▲ = carbon tetrafluoride (CF_4) (Miller, Wilson and Smith, 1978); ⊙ = nitrogen (N_2) (Miller and Wilson, 1978).

To summarize, the critical volume hypothesis stated that all anaesthetics acted at the same molecular site. It has one main predictive feature, namely that for a given increase in the total pressure, the percentage increase in anaesthetic required to maintain a constant level of anaesthesia should be the same for all agents. Theoretically this should be true to infinitely great pressures; the non-linearity at very high pressures was originally explained as being the result of the adverse physiological effects of increased pressures *per se* (e.g. Green, Halsey and Wardley-Smith, 1977). There is no doubt that our results with short acting i.v. anaesthetics do not support the concept of a single site of action for all anaesthetics. The deviations from the predicted straight line cannot be explained away as caused by pressure alone, since we have found non-linearity at pressures as small as 50 atm.

We have thus developed a modification of the critical volume hypothesis in an attempt to explain the discrepancies in the data of both ourselves and others. It retains the original basic concept of the critical volume hypothesis, namely that anaesthetics expand and high pressures contract a molecular site

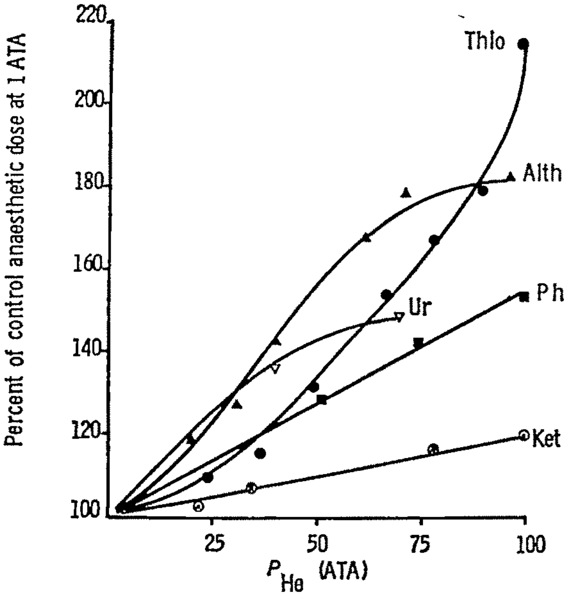

FIG. 3. Representative examples of data for pressure reversal of non-inhalation anaesthetics in rats and mice. x axis—As figures 1 and 2; y axis—as figure 2. Mice data for phenobarbitone (Ph ■) and urethane (Ur ▽) with anaesthesia defined as loss of righting reflex (data from Miller and Wilson, 1978). Rat data for Althesin (Alth ▲), thiopentone (Thio ●) and ketamine (Ket ⊙) with anaesthesia defined as loss of response to electrical stimulus (data from Bailey et al., 1977; Halsey, Wardley-Smith and Green, 1978).

of action, but differs from it in a number of fundamental ways. We have provisionally termed it the multi-site expansion hypothesis; it is based on all the current intact animal data of both ourselves and other workers, and can be best summarized in the following tenets.

(1) General anaesthesia can be produced by the expansion of more than one molecular site, and these sites may have differing physical properties.

(2) The physical properties of a molecular site may themselves be influenced by the presence of anaesthetics or pressure. We believe that the most plausible receptor site characteristic which may change is the compressibility.

(3) The molecular sites do not behave as if they were bulk solvents, but have a finite size and a limited degree of occupancy.

(4) Pressure itself need not necessarily act at the same site as the anaesthetic. Depending on the anaesthetic, one of the sites may predominate in determining the interaction with pressure.

(5) The molecular sites for anaesthesia are not perturbed by a decrease in temperature in a manner analogous to an increase in pressure.

A more detailed discussion of the multi-site expansion hypothesis, and the evidence on which it is based, can be found elsewhere (Halsey, Wardley-Smith and Green, 1978) together with the predictive features by which it can be tested. Although the multi-site expansion hypothesis is more complex than the critical volume theory, it seems to us to be necessary to explain all the current pressure–anaesthetic data. However, it should not be regarded as an alternative to the molecular theories of anaesthesia based on lipid fluidity. Phase changes are accompanied by an increase in volume, and thus are susceptible to pressure reversal (Trudell et al., 1973, 1975).

LIPID CHANGES

The correlation studies and high pressure experiments cannot provide a *detailed* molecular hypothesis about how general anaesthetics may modify the many membrane functions which are potentially important in the transmission of nerve impulses. There have been a number of studies on *in vitro* nerve preparations and isolated components of synaptic junctions, but it is difficult to interpret these data in terms of the underlying molecular events or to extrapolate the results to the *in vivo* integrated nervous system. It has proved more productive to study various simplified lipid models of nerve membranes. These are an oversimplification of the *in vivo* system, but it should be possible to separate out the several molecular changes that are produced by anaesthetics and decide which of these are likely to be critical in the production of general anaesthesia.

The lipids in membranes are now thought not only to provide the basic permeability barrier, but also to influence the activity of proteins which control ionic and neurotransmitter fluxes. The important properties of lipids in controlling protein activities appear to be their ability to move and rotate within the basic bilayer membrane structure. The fluidity or degree of order of the lipids has been shown, for example, to control the activity of the protein of the calcium pump (see review by Lee, 1975). This fluidity can be measured by either nuclear magnetic resonance studies of the lipids themselves or electron paramagnetic resonance studies of marker compounds incorporated into the bilayer. Both techniques are sensitive to the fluidity of the environment around the particular part of the molecule being studied. In pure lipid preparations it has been found that as the temperature is increased there is a general increase in fluidity; at a specific temperature there is a sudden step change when the fluidity increases dramatically. Below this temperature the lipids are described as being in the ordered gel state; above this temperature the fluidity of the lipids are described as being in the disordered liquid crystalline state. This "phase change" can be studied not only by magnetic resonance techniques but also by direct calorimetry, since at the phase change there is a sudden increase in the specific heat (analogous to that which occurs when any solid melts).

For the past 10 years it has been known that anaesthetics alter the fluidity of the lipids and membranes. Metcalfe, Seeman and Burgen (1968) demonstrated that as the concentration of benzyl alcohol in the erythrocyte membrane (or its extracted lipids) was increased, the fluidity of the system also increased. They anticipated more recent concepts by speculating that the presence of the anaesthetic in the membrane produced more and more disorder until finally the protein was exposed. This made available more binding sites in the protein.

Since 1970, there has been a series of theories as to how anaesthetic-induced changes in fluidity of the lipids might influence the activities of the proteins. In general terms, Johnson and Miller (1970) postulated that anaesthetics cause an increase in freedom of movement of the lipid parts of membranes which is associated with an increase in volume which in turn might affect conformational changes in proteins intimately associated with lipid. This paper linked lipid effects with the whole animal data on pressure reversal. Other evidence for the importance of fluidity effects was provided by the demonstration that non-anaesthetic steroids did not alter bilayer fluidity (Lawrence and Gill, 1975). Subsequently, Lee (1976) has taken the association between lipids and proteins one stage further and argued that a sodium channel protein requires an "annulus of lipid" in the more solid gel state to allow activity. Anaesthetics fluidize this lipid, causing the protein to relax into an inactive conformation.

There have been a number of studies demonstrating that anaesthetics shift the phase transition to a lower temperature (Trudell, Payan and Chin, 1974) which results in a much larger increase in anaesthetic-induced fluidity at the original phase transition temperature. This has led to a theory based on "lateral phase separations" (Trudell, 1977). When a lipid bilayer membrane is at the phase change temperature, both the ordered and disordered phases are in equilibrium with each other. At this point any change in internal pressure in the system (produced, for example, by conformational changes in proteins) can be accommodated by shifting the equilibrium position—that is there is "lateral compressibility". If the position of the phase change is shifted by anaesthetics, the equilibrium between the two phases is also shifted so that one of them is no longer present. When only one phase is present the ability of the system to accommodate volume changes is much reduced and the environment of the protein becomes more rigid with respect to lateral expansion (Hanukoglu and Trudell, 1977).

The hypotheses summarized so far have considered the effects of the lipid environment on the functioning of individual proteins. However, this is an over-simplification in that, *in vivo*, groups of a particular type of protein function together in a co-operative manner. The energetic links between these proteins are probably provided by the lipids between them, which themselves are grouped together in clusters either in the gel or in the liquid state. If these gel or liquid crystal clusters are reduced below a critical size then the co-operative linkage between the proteins is disrupted. Experiments with halothane and enflurane in simple lipid systems using differential scanning calorimetry have demonstrated that not only is the fluidity altered but also lipid co-operativity and hence cluster size is reduced (Mountcastle, Biltonen and Halsey, 1978).

Two independent groups have recently put forward an entirely different concept as to how lipids may affect protein function (Ashcroft, Coster and Smith, 1977; Haydon et al., 1977; Hendry, Urban and Haydon, 1978). They proposed that the thickness of the lipid bilayer is increased by anaesthetics, which prevents the protein pore from adequately spanning the membrane. Their evidence for this phenomenon, which is based on electrical measurements of lipid films, is controversial because other techniques—such as x-ray and neutron diffraction (Franks and Lieb, 1978)—indicate that at anaesthetic concentrations there are no significant changes in membrane thickness.

In addition to the discussions about the alternative hypotheses, there are at least two areas of anaesthetic actions on lipids which are controversial: the effects of varying the anaesthetic concentration and the lipid composition. For example, different groups of workers have found that "clinical concentrations" of halothane increase lipid fluidity (Vanderkooi et al., 1977), decrease fluidity (Rosenberg, Gripenberg and

Jansson, 1977) or have no effect (Boggs, Young and Hsia, 1976). The confusion is probably caused by three factors. First, some of the techniques used for studying fluidity are inherently insensitive to small changes and for this reason the early workers (e.g. Trudell, Hubbell and Cohen, 1973) used high concentrations of the agent. However, more sensitive techniques, such as differential scanning calorimetry, have clearly demonstrated changes in lipid fluidity and other parameters at partial pressures well below the clinical range (Mountcastle, Biltonen and Halsey, 1978). The second factor is that Rosenberg and his colleagues have found that increasing anaesthetic concentrations can have a biphasic effect on lipid fluidity—first ordering the system and then fluidizing it (Rosenberg, Eibl and Stier, 1975; Rosenberg, Gripenberg and Jansson, 1977). Thus the problem of choosing the appropriate anaesthetic concentration is qualitative as well as quantitative. The third factor is the lipid composition. For example, pentobarbitone and the other anaesthetics can either decrease or increase the fluidity of phosphatidylcholine bilayers depending on their cholesterol content (Miller and Pang, 1976). However, when the cholesterol content exceeded 26% all the agents studied increased fluidity (Pang and Miller, 1978).

There have been some recent studies with the alcohols which have shown that the short-chained compounds increase fluidity whereas those with more than 10 carbon atoms in the chain decreased fluidity (Richards et al., 1978). However, as yet these studies have not been extended to a wide range of lipid compositions and alcohol concentrations. Another study (Pringle and Miller, 1978) with two isomers of tetradecenol demonstrated that both compounds increase the fluidity of bilayers but change the phase transition temperature in opposite directions. Since the two alcohols are equipotent for tadpole anaesthesia, the evidence appears to favour a simple fluidity hypothesis. In all the alcohol studies just mentioned, the width of the transition peaks was not measured and so the potential importance of co-operativity changes has not yet been assessed.

PROTEIN CHANGES

Anaesthesia may result from a direct interaction between anaesthetics and hydrophobic areas of proteins in addition to the effects on membrane lipids. Some workers have considered only the first part of this hypothesis and have argued the case for the critical site of anaesthetic action being exclusively in the proteins. However, we believe that this is a false distinction and there is considerable indirect evidence that the molecular mechanisms of anaesthesia involve the majority of the components of the neuronal membrane.

In order to prove this hypothesis it is necessary to study the membrane components separately and together. However, at the moment it is difficult to isolate and purify the various neuronal membrane proteins. For this reason the work on proteins has not advanced dramatically since Allison reviewed the subject in 1974. Woodbury, D'Arrigo and Eyring (1975) carried out a theoretical analysis of some of the general anaesthetic data and concluded that direct protein effects predominated. Their analysis was based in part on data from bacterial luciferase, which is a well-established model of a protein system for anaesthetic action. Luciferase used to be thought to be a good example of a protein unaffected by membrane lipids, but recent studies have demonstrated that this is not the case (King and White, 1976) and so Woodbury's analysis is not as convincing as it might be.

The alternative approach of using model protein systems has proved useful in establishing the basis for anaesthetic–protein interactions (Brown, Halsey and Richards, 1976). Nuclear magnetic resonance studies of volatile anaesthetics altering the structure of haemoglobin (Halsey, Brown and Richards, 1978) have provided the first direct evidence that anaesthetics can interact with hydrophobic pockets in proteins and the site(s) appear to behave as simple bulk solvents in terms of their solubility characteristics. The conformational changes produced by such hydrophobic interactions can be transmitted and detected in non-hydrophobic areas of the protein. The fact that conformational effects specific to individual anaesthetics are also observed in the same protein (Barker et al., 1975) is a potential explanation of the many selective actions of different anaesthetics.

Haemoglobin is only a *model* protein, since there is no evidence that it is concerned with the mechanisms of general anaesthesia. Another protein of potentially greater neurophysiological importance is the acetylcholine receptor isolated from stingrays. The electric organs in these fish have very concentrated receptor proteins and thus it is possible to purify the material sufficiently for biochemical and biophysical experiments. Several groups of workers have started to study the anaesthetic interactions, and it has been demonstrated that the clinical volatile anaesthetics can dramatically facilitate a structural change of acetylcholine receptor protein induced by carbamoylcholine (Young et al., 1978). These experiments have been carried out with some of the membrane lipids still associated with the protein and it appears that this is a case where both components of the membrane contribute to the overall effect.

FUTURE RESEARCH

The present position is that we know a considerable amount about anaesthetic effects on lipids and it should be possible to distinguish between the alternative hypotheses on the way these changes are transmitted to functional proteins. We know considerably less about direct effects on membrane proteins and advances in this area depend on advances in the basic techniques for studying complete membranes. It is probable that interest will shift to include other aspects in synaptic transmission, such as the role of calcium and synaptic vesicle fusion processes. When the anaesthetic actions on the individual and integrated components of the synaptic functions have all been studied it may be possible to decide which are the predominant disruptions critical in general anaesthesia.

The correlation studies will probably continue to be refined, but it is unlikely that any radically new concepts will emerge. The high pressure experiments have demonstrated that the *in vivo* molecular mechanisms are more complex than was thought 3 years ago. Future pressure work will be concerned with producing a more detailed theory that links up with the membrane lipid and protein hypotheses.

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ENFLURANE

G. W. BLACK

When halothane and methoxyflurane were introduced into clinical practice in 1956 and 1961 respectively it was assumed that they were inert substances eliminated from the body in an unchanged state (Cohen, 1971). It is now known, however, that some metabolic breakdown of these agents does occur and concern has been expressed that their biotransformation products may exert toxic effects on organs such as the liver and kidney. Largely because of the possible hazards of hepatitis and nephrotoxicity which may be associated with the administration of halothane and methoxyflurane, much interest has been shown in newer and more inert volatile anaesthetic agents. In addition, the fact that personnel in operating and recovery rooms may be at risk because of atmospheric contamination with subanaesthetic concentrations of inhalation agents is another reason for seeking more stable compounds.

In general, it appears that ethers are more likely to be useful anaesthetic agents than are hydrocarbons (Vitcha, 1971). They cause less cardiovascular depression and tend to maintain normal heart rhythm even in the presence of increased concentrations of catecholamines. Methyl ethers have given the most promising results, and the two compounds which have received closest attention—enflurane (Ethrane) and its isomer, isoflurane (Forane)—are members of this series.

Enflurane was found to be easier to synthesize and purify than isoflurane, and the first clinical evaluations were made by Virtue and others (1966) and Dobkin and associates (1968), who reported that it was an efficient volatile anaesthetic with properties largely comparable to those of halothane. Further extensive clinical trials followed these preliminary assessments and enflurane has been used in the United States for the past 8 years. It is now widely used in many countries and is generally regarded as a satisfactory inhalation agent for a variety of surgical procedures.

CHEMICAL AND PHYSICAL PROPERTIES

Enflurane is 2 chloro-1,1,2,-trifluorethyl-difluoromethyl ether. Its chemical structure and physical properties are compared with those of halothane and methoxyflurane in figure 1 and table I.

It is a potent and pleasant-smelling colourless liquid, stable in the presence of metals, alkali and indirect natural light, preservative being unnecessary. Mixtures of enflurane and oxygen are non-inflammable and non-explosive in all proportions.

PHARMACOKINETICS

The uptake, distribution and elimination of inhalation anaesthetics depend largely on certain of their physical characteristics. The blood/gas partition coefficient of enflurane is small and this ensures rapid equilibrium between alveolar and arterial partial pressures resulting in quick induction of and emergence from anaesthesia. Studies of the uptake and elimination of enflurane and halothane in animals and in man show that during the first few minutes of anaesthesia the uptake of the former is much more rapid, while after 15 min the two slopes become similar. Multi-compartment analyses of the uptake and elimination curves of the two agents show a large difference in the slope of the slowest compartment which may be accounted for by the lesser fat solubility of enflurane (Torri et al., 1972). The rate of uptake of enflurane in man during a steady state and the inhalation of 2% vapour has been estimated to be about 700 μg min^{-1} m^{-2} body surface (Huse and Kohler, 1974), and mean blood concentrations at varying levels of narcosis range from 110 to 280 μg ml^{-1} (Scrascia, Magalini and Beccia, 1973). A simple and reliable method for the estimation of enflurane concentrations in whole blood has been described by Toner and colleagues (1977). The quantitative uptake of enflurane at equipotent concentrations is 45–60% greater than that of halothane, the difference being largely accounted for by its lower potency and solubility (F. E. Bennetts, 1979, personal communication).

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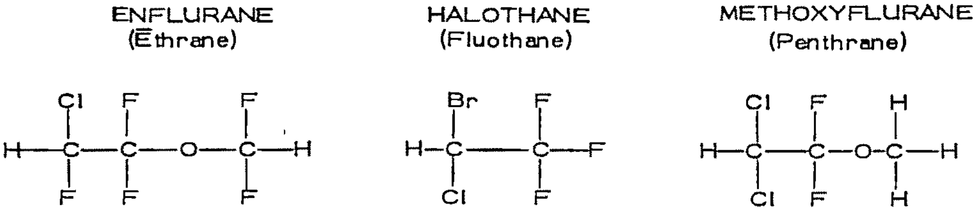

FIG. 1. Chemical structure of enflurane, halothane and methoxyflurane.

TABLE I. *Some physical properties of enflurane, halothane and methoxyflurane*

Properties	Enflurane (Ethrane)	Halothane (Fluothane)	Methoxyflurane (Penthrane)
Molecular weight	184.5	197.4	165.0
Boiling point (at 760 mm Hg)	56.5 °C	50.2 °C	104.7 °C
Vapour pressure	175 (20 °C) 356 (37 °C)	243 (20 °C) 480 (37 °C)	25 (20 °C) 56 (37 °C)
Partition coefficients (at 37 °C)			
Blood/gas	1.9	2.3	13.0
Brain/gas	2.6	4.1	22.1
Fat/gas	105	185	890
Muscle/gas	3.0	6.0	20.0
Oil/gas	98.5	224	930
Water/gas	0.8	0.7	4.5
Minimum alveolar concn (MAC)			
in oxygen	1.7	0.75	0.16
in 70% N_2O	0.57	0.29	0.07

The minimum alveolar concentration (MAC) of enflurane in man is 1.68 (Gion and Saidman, 1971), which indicates that it is only half as potent as halothane (MAC 0.8). In general, greater concentrations of volatile agents are needed in children, and bearing in mind that the MAC value for halothane in infants is about 1.08% (Gregory, Eger and Munson, 1969), it is not surprising that they need very great concentrations of enflurane for adequate anaesthesia.

METABOLISM AND TOXICITY

It has become increasingly clear during the past decade that a close relationship exists between the metabolism of inhalation anaesthetics and their possible toxic effects. Fluorinated ethers such as methoxyflurane and enflurane are probably broken down in the liver with the production of non-volatile end products which are excreted in the urine. The increases in serum inorganic fluoride ion concentrations associated with methoxyflurane anaesthesia have been shown to be nephrotoxic in man (Mazze, Trudell and Cousins, 1971), and it is evident that the extent of breakdown of enflurane into fluoride metabolites is of the utmost importance when considering its potential for producing organ toxicity.

Renal effects

The degree of metabolic breakdown of an inhalation anaesthetic depends to a large degree upon its tissue solubility and because enflurane is relatively insoluble it is not surprising that it is biodegraded to a lesser extent than other agents. Halsey and his associates (1971) found that there was considerable hepatic metabolism of halothane and methoxyflurane in miniature swine, while little or none occurred with enflurane. In studies of Fischer-344 rats, Barr and his colleagues (1974) found mean peak serum inorganic fluoride concentrations of 44 μmol $litre^{-1}$ and 56 μmol $litre^{-1}$ after 6 and 10 h exposure to 2.5% enflurane respectively, compared with 66 μmol $litre^{-1}$ following 1.5 h of 0.25% methoxyflurane anaesthesia. The rats developed vasopressin-resistant polyuric renal dysfunction at these fluoride concentrations, which peaked earlier and returned to control values sooner with enflurane than with methoxyflurane. It was also noted that enzyme induction with phenobarbitone did not increase the defluorination of enflurane nor accentuate its nephrotoxicity (see below). Although these results suggest that enflurane is likely to impair renal function in animals they may not apply to man. As with other agents, the metabolism of enflurane is influenced by species, sex and individual variation, these differing responses being reflected by alterations in serum inorganic fluoride concentrations (Hitt et al., 1975). It would appear that, when considering the metabolism of enflurane or indeed any volatile anaesthetic, more reliable information can be obtained from clinical investigation. In a study of seven healthy females Chase and colleagues (1971) reported that 82.7% of absorbed enflurane was exhaled unchanged and 2.4% was excreted in the urine as non-volatile fluorinated metabolites. In a group of 10 surgical patients a mean peak serum inorganic fluoride concentration of 22.2 μmol litre^{-1} was noted 4 h after enflurane anaesthesia (Cousins et al., 1976), and these findings are confirmed in another clinical study in which peak serum fluoride concentrations of 16 μmol litre^{-1} were reached 4 h after anaesthesia, returning to normal on the 4th day after operation (Corall, Knights and Strunin, 1977). Hitt and Mazze (1977) presented clinical data which suggest that enflurane metabolism occurs mostly during the period after surgery, proceeding at maximum rates even when blood concentrations are very small. When small concentrations of enflurane (1.3%) are inhaled for a short time (1 h) serum fluoride concentrations increase to a mean maximum of only 7 μmol litre^{-1} 1 h after anaesthesia, which means that danger of renal damage is remote following short periods of narcosis (Sakai and Takaori, 1978). In general, maximum serum fluoride concentrations after enflurane anaesthesia are not unduly great, usually about 25 μmol litre^{-1}, and they decline more rapidly than after exposure to methoxyflurane. In these circumstances it would not seem unreasonable to assume that the danger of enflurane-induced renal damage is slight because serum concentrations of 50 μmol litre^{-1} are usually necessary to cause fluoride nephrotoxicity (Cousins and Mazze, 1973). However, the critical concentration may be smaller than was previously suspected, Mazze, Calverley and Smith (1977) having observed a 25% reduction in maximum urine concentrating ability following enflurane anaesthesia when the average serum fluoride concentration was only 15 μmol litre^{-1}. Such a defect may not be of any clinical significance when renal function is normal, but the findings indicate that even relatively small threshold fluoride concentrations may temporarily alter renal function and it is possible that surgical patients with pre-existing renal disease could be harmed by the additional fluoride load.

Studies of the renal effects of enflurane in man show that renal blood flow, glomerular filtration rate and urinary flow rate are reduced by 23, 21 and 33% respectively (Cousins et al., 1976; Jensen et al., 1978), and are of the same order as occur with other volatile anaesthetic agents.

The role of enzyme induction in the causation of renal dysfunction associated with enflurane anaesthesia is not clear. *In vivo* studies in Fischer-344 rats show that although enzyme induction with phenobarbitone and phenytoin increases defluorination after methoxyflurane anaesthesia, this does not occur following exposure to enflurane (Hitt and Mazze, 1977). These findings suggest that enzyme-inducing drugs do not increase the hazard of renal impairment with enflurane, at least in some species, but this may not apply to the clinical situation. In a group of eight patients, 0.5 MAC enflurane given for 2 h, following a previous identical exposure 1 week earlier, did not cause any increase in urinary inorganic fluoride excretion (Norgate, Sharp and Cousins, 1976), and it would seem that, as in animals, enzyme induction in man does not result in significant increases in enflurane defluorination.

The effects of enflurane in anephric patients and in those with severe renal disease were compared with a group of healthy control subjects, and it was found that maximum serum fluoride concentrations did not alter significantly in the three groups (Carter, Heerdt and Acchiardo, 1976). The authors believe that the uptake of fluoride by bone is the main determinant of serum concentrations after low-dose enflurane anaesthesia, and that toxic effects on the kidney are unlikely, even in the complete absence of renal function. Although renal failure following enflurane anaesthesia has been reported (Eichhorn et al., 1976), it seems unlikely that the agent would adversely affect the normal kidney unless high vapour strengths are inhaled for prolonged periods. However, it is possible that variations in serum fluoride concentrations following enflurane anaesthesia may have a genetic basis, which would explain unpredictability of its metabolism in man (Hitt et al., 1975). Care should be taken in patients with pre-existing renal disease and in situations in which other intraoperative factors could compromise kidney function.

Hepatic effects

Extensive animal and clinical study has failed to detect any significant alteration in liver function following exposure to enflurane. In general, only minimal changes in serum transaminases, alkaline phosphatase and bilirubin were found (Lebowitz, Blitt and Walts, 1970; Linde et al., 1970). In a recent study designed to determine comparative toxicities, suspensions of rat hepatocytes were incubated with varying concentrations of different halogenated anaesthetic agents (Stacey, Priestly and Hall, 1978). Toxicity, as determined by leakage of intracellular potassium and alanine aminotransferase, was most pronounced with chloroform and methoxyflurane, and significantly exceeded that of halothane after 20 min of incubation. Enflurane, however, did not affect potassium or alanine aminotransferase release, even after 60 min of incubation, at which time halothane toxicity was markedly increased. The toxic effects of halogenated inhalation anaesthetic agents as measured in this *in vitro* preparation appear to be of the same comparative order as their potential to cause clinical hepatotoxicity. McLain and colleagues (1977) found no toxic effect in the liver of rats pretreated for 10 days with phenobarbitone and then exposed to enflurane with hypoxia for 2 h while, in contrast, 90% of rats treated in the same way with halothane developed hepatic necrosis. Prolonged periods of enflurane anaesthesia (9 MAC hours) in young fit volunteers caused only slight changes in liver function test values (Eger, Calverley and Smith, 1976).

There are a few clinical reports of impairment of liver function following enflurane anaesthesia (Denlinger, Lecky and Nahrwold, 1974; Sadove and Kim, 1974), but the influence of factors such as virus hepatitis and large blood transfusion cannot be excluded.

Enflurane is often used instead of halothane when repeated administrations are necessary, although there is no clear evidence that it is a safe alternative. It would appear that comprehensive prospective studies are required to evaluate the extent of the relationship between repeated administration of halothane and enflurane and the onset of liver dysfunction. Such studies are expensive, but the subject is of paramount importance and they would appear to be necessary and justifiable. In a prospective study of hepatocellular function after repeated exposure to halothane or enflurane in 99 black women requiring radiation for cervical carcinoma, changes in serum transaminase concentrations were minimal and the authors concluded that in this group of patients enflurane appears to be a suitable alternative to halothane (Allen and Downing, 1977). In a preliminary report of another trial, 37% of patients who received halothane repeatedly developed abnormal liver function tests, compared with 14% of patients who received repeated enflurane anaesthesia, and the trend towards disordered liver function with the number of administrations was more pronounced with halothane than with enflurane (Johnston et al., 1979). In this study there was little alteration in liver function test patterns after repeated enflurane anaesthesia, but the data are not yet complete nor have they been fully analysed, and it is not possible to state unequivocally that the severe form of hepatitis sometimes associated with halothane will not occur with enflurane. Nevertheless, no case of what could be unreservedly called "enflurane hepatitis" has appeared in the literature, and these initial findings suggest that enflurane may well be a suitable alternative to halothane when repeated inhalation anaesthesias are indicated.

Carcinogenicity and teratogenicity

Although the evidence of a relationship between anaesthetic agents and human cancer is limited and mostly of epidemiological nature, any volatile anaesthetic in clinical use should be carefully examined for carcinogenic properties. Mutagenicity tests, which are suitable for carcinogenicity screening, show that there is no significant increase in the number of mutant colonies compared with controls after 24 h of exposure of Chinese hamster cells to 1.5–6.5% enflurane, and no damaged chromosomes were seen in metaphase cells on slides (Sturrock, 1977). In a study of halogenated ethers, in which enflurane, methoxyflurane, isoflurane and fluroxene were tested for mutagenic activity, only fluroxene was positive (Baden et al., 1976).

The effects of trace elements of enflurane in pregnancy are also important because of reports of atmospheric pollution causing spontaneous abortion and congenital abnormalities in personnel working in operating theatre areas. Prolonged daily exposure to small (10 p.p.m.) and large (64 p.p.m.) subanaesthetic concentrations of enflurane in pregnant rats caused no significant differences in weights of the offspring or litter sizes. It may be concluded from this work that enflurane has little effect in rat pregnancy and postnatal development (Strout et al., 1977). However, in studies of other laboratory animals in which the toxicities of subanaesthetic concentrations of different agents were compared, enflurane was found to have a dose-related detrimental effect on weight gain, although the smallest concentration used (0.32 MAC) caused minimal weight changes and far less hepatic damage than 0.27 MAC halothane (Stevens et al., 1977). The available evidence suggests that there is little risk of carcinogenesis, mutagenesis or teratogenesis associated with the clinical use of enflurane.

CARDIOVASCULAR SYSTEM

Haemodynamic changes

As with other halogenated compounds, there is usually a decrease in arterial pressure when enflurane is inhaled, the degree of hypotension being proportional to the concentration of inhaled vapour. This could be a result of vasomotor centre inhibition, altered baroreceptor function, suppressed sympathetic nervous activity, impaired left ventricular function or reduced systemic vascular resistance, any or all of these being responsible. Enflurane produces haemodynamic effects comparable to those of halothane, but opinion differs regarding the relative extent of the cardiovascular depression they produce. Also, it is difficult to reconcile the conflicting data from the many studies of the cardiovascular effects of enflurane. Species, preanaesthetic medication, different MAC values, alterations in Pa_{CO_2} and the effects of surgery have to be differentiated from the pharmacological effects of enflurane *per se*. A study of the inotropic effect of enflurane on the cat papillary muscle suggests that the newer agent may cause less myocardial depression than halothane (Shimosato et al., 1969), and earlier clinical reports indicated that circulatory changes were only minimal during enflurane anaesthesia. Marshall and his colleagues (1971) observed that, in the presence of hypocarbia, normocarbia and hypercarbia, cardiac output and arterial pressure were well maintained during light levels of enflurane anaesthesia. They found that the awake circulatory response to the inhalation of carbon dioxide was unaltered during enflurane anaesthesia and concluded that this signified only minimal impairment of myocardial contractibility and sympatho-adrenal activity. In another clinical investigation in 10 volunteers enflurane diminished stroke volume, although cardiac output was maintained by an increased heart rate in spite of reductions in systemic vascular resistance (Levesque et al., 1974). In the absence of tachycardia, however, decreases of 20% in cardiac output and arterial pressure have been reported (Graves and Downs, 1974).

Cardiovascular depression was only of a moderate degree in many of these studies, probably because small vapour strengths were used for short periods of time. There is clear evidence, however, that when high concentrations are inhaled there may be pronounced impairment of cardiac function. In trained dogs with chronically implanted transducers 3.6% enflurane caused depression of myocardial function perfusion and metabolism. Halothane 2 MAC resembled enflurane 1.6 MAC, suggesting that the cardiovascular dose-response curve for enflurane was steeper than for halothane (Merin, Kumazawa and Luka, 1976). In other canine studies it was noted that, in equipotent concentrations, enflurane produced marginally more diminution of left ventricular function than halothane and caused a dose-dependent reduction of arterial pressure, cardiac output and myocardial contractility (Horan et al., 1977).

Calverley and colleagues (1975) found that cardiac output was depressed in volunteers inhaling 1 MAC enflurane, 2 MAC inducing unacceptable cardiovascular depression and a lack of adaptation of the circulation with time. The circulatory effects were more marked during artificial ventilation with normal Pa_{CO_2} values than during spontaneous breathing with hypercarbia.

Conflicting clinical reports of circulatory changes during enflurane anaesthesia may sometimes be attributed to the influence of the associated surgery. In a study of 10 surgical subjects, Santesson and his colleagues (1978) found decreases in both cardiac output and systemic vascular resistance during normocapnic 1.5 MAC enflurane anaesthesia. With the commencement of surgery cardiac output increased but vascular resistance remained unchanged, possibly because of an alpha-adrenoceptor blocking action. In some clinical studies enflurane caused little change in cardiac index because a pronounced increase in heart rate compensated for the diminution in stroke volume. It would appear that if the heart rate is rapid before the induction of anaesthesia, enflurane tends to cause some cardiac slowing, while if it is slow beforehand then an increase may occur. In echocardiographic studies in 20 healthy subjects, left ventricular function was impaired by halothane but not during enflurane anaesthesia. Although the short period of exposure (12 min following induction) limits the usefulness of the data, the authors emphasize the safe and non-invasive nature of the technique (Rathod et al., 1978).

Reductions of mean arterial pressure of the order of 10% were noted 10 min after the commencement of enflurane anaesthesia in a group of 150 surgical patients (Black, Johnston and Scott, 1977). Although the frequency of this hypotension was reduced by the onset of surgical procedure it remained a prevalent feature throughout the period of operation in 51% of the patients. Excessive decreases in arterial pressure respond to reductions in the concentration of inhaled enflurane and to the administration of i.v. fluids.

Enflurane causes reductions in arterial pressure which may be comparable to or greater than the concurrent decreases in cardiac output, so that total peripheral resistance is unchanged or decreased. Studies of the vasomotor responses of the human forearm to enflurane show that it has a potent vasodilator action on the peripheral vasculature which is more pronounced than with halothane at equipotent concentrations (M. G. Scott, 1979, personal communication). Although reductions in cerebral (Smith and Wollman, 1972), coronary (Merin, Kumazawa and Luka, 1976) and renal (Lhoest, 1976) vascular resistance are not pronounced, there is no evidence to indicate compensatory vasoconstriction in other areas of the body during enflurane anaesthesia.

It would thus appear that enflurane produces cardiovascular depression by a direct action on the heart and also by causing alterations in the capacity of the circulatory bed. However, it also interferes with circulatory homeostasis, and sympathetic activity is suppressed by aortic depressor nerve stimulation (Skovsted and Price, 1972). Also, like other inhalation anaesthetics, enflurane inhibits the acetylcholine-mediated release of noradrenaline at sympathetic nerve endings throughout the body (Gothert and Wendt, 1977). The addition of nitrous oxide has only minimal effects on the circulatory changes caused by enflurane and there is no evidence of the adrenergic stimulation seen with other potent inhalation agents (Smith et al., 1978). It is not known why the sympathomimetic response to nitrous oxide is pronounced with halothane, an agent which induces only minimal sympatho-adrenal activity and yet is absent during enflurane anaesthesia.

Changes in heart rate and rhythm

Many of the changes in cardiac rate and rhythm occurring during anaesthesia may be explained on the basis of altered autonomic balance, a preponderance of vagal or sympathetic activity producing characteristic changes.

Enflurane causes a decrease in heart rate in the dog (Atlee and Rusy, 1977), but changes in man vary, Marshall and colleagues (1971) finding no alteration and Levesque and his colleagues (1974) reporting significant increases. In a recent clinical study a substantial increase (12%) in heart rate was noted during 1.5 MAC enflurane anaesthesia compared with a marked decrease (14%) when an equipotent concentration of halothane was inhaled (Heiberg, Wiberg-Jorgensen and Skovsted, 1978). Although enflurane depresses sympatho-adrenal activity, Krishna and Paradise (1977) report that it possesses a direct positive chronotrophic effect on isolated atrial preparations and this, together with a possible vagolytic action, could account for the increases in cardiac rate observed clinically.

The appearance of spontaneous arrhythmias is uncommon during enflurane anaesthesia. When ventricular ectopic contractions occur they are often of short duration and may be abolished by improving pulmonary ventilation.

Studies made in dogs suggest that enflurane sensitizes the myocardium to the effects of catecholamines and the frequency of severe arrhythmia following a challenge with adrenaline was found to be comparable to that associated with halothane (McDowell, Hall and Stephen, 1968). The results of several clinical studies, however, indicate that changes in cardiac rhythm rarely follow the careful subcutaneous injection of adrenaline during enflurane anaesthesia. A very much lower frequency of cardiac irregularities is found when adrenaline is injected during enflurane anaesthesia than with halothane (Reisner and Lippmann, 1975), and in the case of enflurane the amount of adrenaline needed to induce ectopic ventricular contractions was 10.9 $\mu g\ kg^{-1}$ compared with 6.7 $\mu g\ kg^{-1}$ during isoflurane anaesthesia and 2.1 $\mu g\ kg^{-1}$ when halothane is being inhaled (Johnson, Eger and Wilson, 1976). There is, however, a wide variation in patient response to adrenaline during enflurane anaesthesia and occasionally patients may develop ventricular arrhythmia at much smaller doses than would be anticipated (Horrigan, Eger and Wilson, 1978). It should be remembered that the blood catecholamine titre may readily be increased by factors such as light anaesthesia and hypercarbia, and in these circumstances the absorption of even small quantities of injected adrenaline may have serious consequences.

Reduction in heart rate and depression of ventricular automaticity are thought to play an important role in the production of arrhythmia associated with the use of inhalation anaesthetics with a hydrocarbon structure (Reynolds, Chiz and Pasquet, 1970). There is evidence, however, that ventricular arrhythmia induced by adrenaline during anaesthesia is caused by re-entry of excitation, a mechanism which requires altered conduction (Zink, Sasyniuk and Dresel, 1975). In studies made in dogs enflurane, like halothane, prolongs A–V conduction time but, in contrast to halothane, has no effect on ventricular conduction time (Atlee and Rusy, 1977). This may partly explain why there is less tendency for adrenaline to cause disordered cardiac rhythm during enflurane anaesthesia than with halothane.

Enflurane has been recommended as the anaesthetic of choice for the surgical removal of phaeochromocytoma tumours because it is less likely to induce cardiac arrhythmia than halothane and because the danger of nephrotoxicity is less pronounced than with methoxyflurane (Kopriva and Eltringham, 1974; Ortiz and Diaz, 1975). In one case report normal sinus rhythm persisted during enflurane anaesthesia while a phaeochrome tumour was removed, in spite of 10-fold increases in plasma catecholamine concentrations (Kreul, Dauchot and Anton, 1976).

RESPIRATORY SYSTEM

Clinically used concentrations of enflurane are non-irritant to the respiratory tract, and surgical levels of anaesthesia can readily be attained. Increases in salivation and tracheobronchial secretions are uncommon and the use of antisialogogue drugs is not essential (Dobkin et al., 1968). Because of its non-irritant nature, the inspired vapour concentration can be increased with little risk of coughing, laryngospasm or bronchospasm, although the latter complication has been reported (Lowry and Fielden, 1976). However, enflurane may cause respiratory depression particularly when higher concentrations (more than 3%) are being inhaled before the commencement of surgery. This is usually the result of a diminished tidal volume, respiratory rates remaining unchanged or slightly increased (Linde et al., 1970). Manual control of breathing is required in the presence of decreasing ventilation and, in the case of small infants, pronounced respiratory depression may occur before a satisfactory level of anaesthesia is reached.

The respiratory depression caused by enflurane is more pronounced than with other volatile anaesthetic agents. Rats exposed to enflurane have a smaller respiratory anaesthetic index (i.e. the concentration producing apnoea divided by the concentration required for anaesthesia) than those exposed to methoxyflurane, halothane or isoflurane (Wolfson et al., 1978). Dogs exposed to 1 MAC enflurane or halothane have substantially reduced responses to hypoxia and hypercarbia (Hirshman et al., 1977), although there is no quantitative difference between the two agents at either 1 or 2 MAC. Clinical studies also show that enflurane impairs pulmonary ventilation more than halothane (Munson et al., 1966), or methoxyflurane (Larson et al., 1969) at comparable MAC levels of anaesthesia. Unstimulated volunteers had Pa_{CO_2} 8.1 kPa at 1 MAC, Pa_{CO_2} 9.4 kPa at 1.5 MAC and developed apnoea at 2 MAC enflurane, although this degree of respiratory depression did not persist with prolonged anaesthesia (Calverley et al., 1975). The respiratory depressant effects of enflurane are at least partly antagonized by the reflex effects of surgery and intra-operative Pa_{CO_2} values in excess of 6.7 kPa are uncommon.

CENTRAL NERVOUS SYSTEM

Electroencephalographic (e.e.g.) studies in animals show that enflurane can induce paroxysmal activity (de Jong and Heavner, 1971), a form of e.e.g. pattern usually associated with epileptic disease. Changes of similar nature occur in man and several clinical studies confirm that episodes of paroxysmal activity and periods of suppression are features of e.e.g. tracings during deep enflurane anaesthesia (Clark, Hosick and Rosner, 1971; Neigh, Garman and Harp, 1971). Tonic–clonic twitchings of the muscles of the face and limbs may develop during deeper levels of anaesthesia when the patient is being hyperventilated. These responses, which are exacerbated by hypocarbia and suppressed by hypercarbia, can be readily terminated by reducing the level of anaesthesia and encouraging a return to normocarbia. In a comparative study of the neural effects of enflurane and ether, e.e.g. tracings were made during deep anaesthesia at levels of narcosis which permitted abdominal surgery to be carried out without the need for muscle relaxants (Persson, Peterson and Wahlin, 1978). Episodes of paroxysmal spike activity and periods of suppression were often noted in e.e.g. tracings during enflurane anaesthesia, usually appearing at concentrations in excess of 3%. Similar changes were noted with equipotent concentrations of ether, but they were of shorter duration and much less pronounced. The results of studies by Rosen and Soderberg (1975) suggest that electroencephalographic seizure activity is common in children with moderate hypocarbia inhaling concentrations of 3%

or more, and that with 4% vapour strength there may be generalized epileptic activity of grand mal type. No such e.e.g. activity has been reported in adults, possibly because of differences in cerebral sensitivity between the child and adult and the greater concentrations of enflurane needed in the younger patients. There is general agreement that abnormal e.e.g. patterns are a sign of overdosage and should be abolished by decreasing the concentration of inhaled enflurane and by correcting any existing hypocarbia. E.e.g. studies in a group of 21 children and adults suffering from various forms of epilepsy showed no obvious changes or correlation with enflurane concentration, nor were epileptiform discharges provoked in these subjects (Opitz, Brecht and Stenzel, 1977). Twelve volunteers were exposed to 9.6 MAC hours enflurane anaesthesia, and six developed one or more episodes of e.e.g. seizure activity with tonic-clonic motor movements. All awoke shortly after the cessation of anaesthesia and although e.e.g. changes persisted in varying degree from 6 to 30 days, no *de novo* evidence of epileptiform activity appeared in any of the subjects studied (Burchiel et al., 1977). In a small proportion of subjects inhaling enflurane there may be increases in cerebral activity, indicated by twitchings of the face and limb muscles associated with e.e.g. spiking, signs which are dose related and indicate overdosage. They are abolished by reducing the concentration of inhaled enflurane and by correcting hyperventilation and associated hypocarbia. Although enflurane did not provoke epileptiform discharges in a group of 21 patients suffering from various types of epilepsy (Opitz, Brecht and Stenzel, 1977), it would seem advisable to avoid its use in diseases of this nature.

Fifty per cent reductions in cerebral oxygen consumption occur during the inhalation of 3% enflurane, making it a potent depressor of cerebral metabolism (Smith and Wollman, 1972). Enflurane causes vasodilatation and provided arterial pressure is maintained, then cerebral blood flow is increased (Smith, 1975). However, reductions in cerebral blood flow may follow decreases in arterial pressure. Surgical occlusion of the carotid artery may be associated with decreased cerebral perfusing pressure, but there is no increased morbidity when enflurane is used for the management of patients requiring carotid endarterectomy (McKay et al., 1976).

In a comparison of the intracranial effects of enflurane and halothane in 11 neurosurgical patients there was either no change or small and inconsistent increases in intracranial pressure during enflurane anaesthesia, while significant increases invariably occurred when halothane was inhaled (Cunitz, Danhauser and Gruss, 1976). It has been suggested that enflurane is more likely to induce an increase in intracranial pressure in the presence of a space-occupying lesion (Boop and Knight, 1978), although this conclusion is drawn from studies made in the dog.

Effects on uterine tone and use in obstetric practice

Like other halogenated anaesthetics, enflurane produces a dose-related relaxation of the isolated human uterus (Munson and Embro, 1977), this being slight at 0.5 MAC but pronounced at 1.5 MAC. Other findings show that, although small concentrations of enflurane do not interfere with spontaneous uterine activity, deep anaesthesia may diminish the contractile activity normally induced by oxytocin.

There are several reports of the favourable use of small concentrations of enflurane for induction and maintenance of anaesthesia for Caesarean section, the results being satisfactory for both mother and child. In a series of 50 patients having this operation, features such as absence of factual recall, no undue bleeding and freedom from fetal depression suggested a need for further trial (Coleman and Downing, 1975). Magno, Kjellmer and Karlsson (1976) compared the effects of enflurane and barbiturate anaesthesia in a series of 14 women undergoing elective Caesarean section and found that there was much less tendency to metabolic acidosis in the infant when inhalation anaesthesia was used.

Although enflurane depresses uterine contractility it is generally agreed that the response of the uterus to oxytocin is retained provided that inhalated concentrations of 3% are not exceeded. Some reports indicate that blood loss may be considerable during Caesarean section when enflurane is used, but there is no clear evidence to indicate that it is greater than when other methods of anaesthesia are used.

Muscle relaxation

Enflurane causes a dose-related depression of neuromuscular transmission. Studies of muscle twitch responses to ulnar nerve stimulation in man during enflurane anaesthesia show that with concentrations greater than 2.5% there is direct depression of twitch response with fade and post-tetanic facilitation (Lebowitz, Blitt and Walts, 1970). Neostigmine does not reverse these direct effects of enflurane, which the authors believe are more pronounced than with other volatile anaesthetic agents.

To evaluate this peripheral action, the effect of enflurane on neuromuscular transmission was studied in the rat phrenic nerve–diaphragm preparation by recording intracellular events at the muscle end-plate. Enflurane probably acts at the myoneural junction, because it decreases the magnitude, not the frequency, of miniature end-plate potentials, so that, although the rate of release is not affected, there is a diminished effect on the motor end-plate. Also, the rate of rise of end-plate potential and voltage change needed for membrane depolarization provide further evidence that enflurane acts at the end-plate and post-synaptic membrane (Kennedy and Galindo, 1975).

As might be expected, enflurane produces a marked degree of muscular relaxation and it is often possible to provide satisfactory operating conditions for abdominal surgery without recourse to neuromuscular blocking drugs. However, the greater concentrations of enflurane which are required are liable to cause significant hypotension and perhaps manifestations of increased irritability of the central nervous system, so that the use of muscle relaxant drugs may be a more prudent alternative. When neuromuscular blocking drugs are indicated, smaller than normal doses are often adequate. In a series of 37 surgical patients Fogdall and Miller (1975) concluded that smaller doses of tubocurarine and pancuronium were required for satisfactory relaxation during enflurane anaesthesia than when equi-MAC concentrations of halothane were being inhaled (figs 2, 3). Also, greater alveolar concentrations of enflurane reduced the dose of tubocurarine and pancuronium needed to produce a given degree of muscular paralysis. The augmentation of the action of non-depolarizing neuromuscular blocking drugs by enflurane is more pronounced than with other potent inhalation anaesthetics, the average patient requiring only about half as much tubocurarine as would be needed during halothane anaesthesia (Ali and Savarese, 1976).

Because of the danger of untoward responses to neuromuscular blocking drugs in myasthenic patients requiring surgery, it is suggested that enflurane be used to provide muscle relaxation without resorting to these drugs (Girnar and Weinreich, 1976).

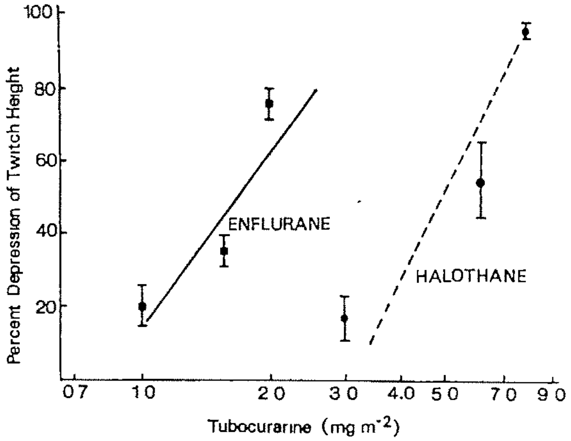

FIG. 2. Dose–response curves for tubocurarine in patients anaesthetized with 1.25 MAC enflurane ($r = 0.84$) or 1.25 MAC halothane ($r = 0.91$), plotted logarithmically. Lines represent analysis of linear regression. (Reproduced from Fogdall and Miller (1975), by permission of the authors.)

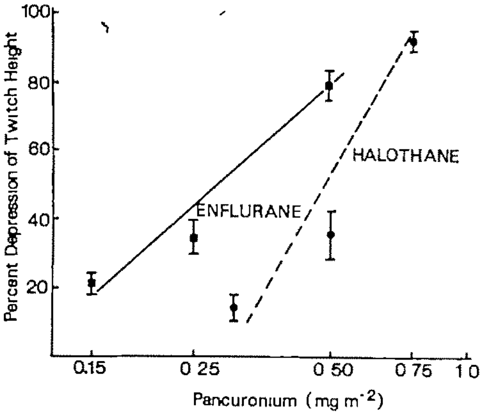

FIG. 3. Dose–response curves for pancuronium in patients anaesthetized with 1.25 MAC enflurane ($r = 0.90$) or 1.25 MAC halothane ($r = 0.92$), plotted logarithmically. Lines represent analysis of linear regression. (Reproduced from Fogdall and Miller (1975), by permission of the authors.)

Effects on intra-ocular pressure

Significant reductions in intra-ocular pressure (i.o.p.) have been reported in young fit patients spontaneously breathing 3–5% enflurane (Radtke and Waldman, 1975). In another investigation 10 healthy adults inhaling 1% enflurane with controlled respiration all exhibited substantial reductions in i.o.p. In a comparable group of 10 subjects 0.5% halothane failed to alter mean i.o.p. significantly and produced varying effects in individual patients (Runciman et al., 1978). These authors conclude that enflurane 1% in combination with nitrous oxide, oxygen and controlled ventilation decreases i.o.p. significantly and is suitable for the management of anaesthesia in ophthalmic practice.

ENFLURANE IN CLINICAL PRACTICE

Administration

Specially calibrated vaporizers should be used when administering enflurane, and the scale settings of these usually range from 0.2 to 5.0% vapour strength. In general, concentrations of 3–4% are required for induction and 1–3% for the maintenance of anaesthesia.

In adults, i.v. induction of anaesthesia usually precedes the inhalation of enflurane given in a mixture of nitrous oxide and oxygen or oxygen only. The concentration of enflurane vapour is gradually increased by 0.5% increments every few breaths until a stable level of surgical anaesthesia is obtained, usually in the range 1–3%. Respiratory depression may occur in the spontaneously breathing patient who is inhaling concentrations greater than 3%, and controlled ventilation may then be indicated. Only minimal concentrations are necessary in patients receiving non-depolarizing neuromuscular blocking drugs.

Enflurane is suitable for both induction and maintenance of anaesthesia in children. They readily accept enflurane given by face mask and it is possible to induce anaesthesia with little excitement or agitation. Enflurane is only about half as potent as halothane and because of its high MAC value it should be given continuously to provide adequate levels of anaesthesia. When anaesthesia is discontinued there is usually a rapid return of consciousness. Enflurane produces little relief from pain after operation, presumably because of its rapid elimination from the body, and there may be an earlier need for analgesics after operation.

Use in outpatient departments

Since many of its physical properties are comparable to those of halothane, it is not surprising that enflurane possesses similar clinical characteristics. Because of its low blood/gas partition coefficient, consciousness is lost quickly, the level of anaesthesia may be controlled easily and the patient awakens shortly after the inhalation of enflurane is discontinued. These features suggest that it would be satisfactory for use in the outpatient department, and comparative studies of postoperative efficiency following brief exposure provide evidence that speed of induction and rate and quality of recovery may be superior to halothane. In a study of 34 healthy volunteers, Korttila and colleagues (1977) found that there was less impairment of psychomotor and driving skills following enflurane than following halothane anaesthesia. These workers also present data showing that inhalation anaesthetics are preferable to i.v. barbiturates for outpatient anaesthesia and confirm the findings of Trieger and Lassner (1975). Writing tests made 10 min after the cessation of anaesthesia in a group of 50 females requiring minor surgery showed that 12% of those who received halothane were unable to write, compared with only 4% of those given enflurane, although these differences were not observed after 60 min (Kessler and Haferkorn, 1977). In a study of 10 male volunteers it was found that subanaesthetic concentrations of enflurane (0.25%) slowed the rate of learning and the adaptation to changes in environmental factors (Bentin, Collins and Adam, 1978), although these do not differ greatly from similar effects produced by other inhalation anaesthetics. Kraut and his colleagues (1978) have evaluated enflurane as an amnesic agent for outpatient dental surgery. They describe a technique for inducing co-operative amnesia with enflurane and oxygen, given by nasal mask, in 31 patients requiring dental surgery in the outpatient department. Using discriminating questions and psychomotor function tests it was found that 69% of the group had complete amnesia while the remainder had only minimal recall. The authors believe that the technique deserves further investigation, and it is possible that the inhalation of low concentrations of enflurane may be of value in the management of burns dressings and obstetric practice.

Advantages and disadvantages

The rapid induction and recovery from enflurane anaesthesia are of particular benefit in the outpatient department and these features, together with the pleasant smell, make it very acceptable to children, although high concentrations are sometimes needed to provide adequate anaesthesia in infants and small children. Also, because of the low blood solubility of enflurane the depth of anaesthesia can be readily altered.

Animal and human studies reveal that the degree of biotransformation of enflurane is much less than with other inhalation anaesthetic agents, perhaps because of its chemical stability and high degree of fluorination. There is increased biotransformation as a result of *in vitro* enzyme induction, but no evidence that patients receiving barbiturates or other drug therapy have increased serum fluoride concentrations after enflurane anaesthesia, nor would it appear that these concentrations increase following a second administration.

Catecholamine "sensitization" of the myocardium is less pronounced than with halothane, and adrenaline carefully injected may be used for haemostatic purposes. Also, the appearance of spontaneous cardiac arrhythmia is uncommon and enflurane is generally regarded as suitable for use in conditions in which increased plasma catecholamine concentrations are anticipated, such as phaeochromocytoma.

Animal and clinical studies show that pronounced upsets of liver function are uncommon after enflurane anaesthesia. Although the situation with regard to repeated administration is not clear, enflurane is often used instead of halothane in order to avoid the possibility of litigation arising from claims for "halothane induced hepatitis". This is understandable, since reports of massive necrosis after enflurane anaesthesia are rare, and because few other suitable alternatives are available. General anaesthetic techniques using neurolept, narcotic or neuromuscular blocking drugs are largely devoid of toxic effects on the liver and kidney, but they may cause undue circulatory and respiratory depression. Also, they are not always suitable for the short procedures in the outpatient department for which anaesthesia has often to be repeated within a few weeks. The choice of volatile anaesthetics was restricted until recently because of the clinical limitations of trichloroethylene and methoxyflurane. Enflurane may play an important role in the management of cases requiring frequent anaesthesia, but this has yet to be determined.

There are, however, some aspects of enflurane anaesthesia which may give rise to concern. Several investigations show that enflurane has a potent depressant effect on the cardiovascular and respiratory systems in the unstimulated subject, especially when high concentrations are being inhaled. In the clinical situation, however, these changes are largely counterbalanced by the reflex effects of surgery, and marked decreases in arterial pressure and tidal volume are not usually a problem during spontaneous breathing. There may sometimes be marked respiratory depression in infants and small children during induction of anaesthesia before satisfactory conditions for surgery are attained.

Although the peak inorganic fluoride concentrations which result from the breakdown of enflurane are generally much smaller than those considered to be nephrotoxic, they vary considerably and it is conceivable that some impairment of renal function could result from the inhalation of high concentrations for a prolonged period. Usually, however, enflurane is rapidly eliminated from the body and exposure of the kidney to the potentially toxic biotransformation process is brief. The effects of enflurane in the diseased kidney have not been fully evaluated and it would seem reasonable to avoid its use in the presence of pre-existing renal disease and in situations which may compromise kidney function.

In a small proportion of cases there may be increased cerebral irritability, indicated by twitchings of the face and limb muscles associated with e.e.g. spiking, signs which are dose-related and indicate overdosage. They are abolished by reducing the concentration of inhaled enflurane and by correcting hyperventilation and associated hypocarbia. Subjects with these manifestations recover from anaesthesia normally, and there is no evidence from animal or human investigation that enflurane causes any permanent upset of central nervous system function. Although enflurane did not provoke epileptiform discharges in patients suffering from various types of epilepsy, it would seem advisable to avoid its use in diseases of this nature.

CONCLUSION

Enflurane is well established in clinical anaesthesia as a useful agent for many surgical procedures. The risks of damage to the kidney and central irritability are small but undesirable features of enflurane. Newer halogenated ethers such as isoflurane and sevoflurane have many excellent properties, but for financial and other reasons they may not become generally available in anaesthetic practice. In the search for the ideal inhalation anaesthetic the most promising compounds will be these with minimal biodegradation, appropriate pharmacokinetics, little cardiovascular or respiratory depression and without toxic effects on the liver, kidney or fetus.

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NEW I.V. ANAESTHETICS

J. W. DUNDEE

Until recently there was little doubt as to what would constitute an "intravenous anaesthetic"—a drug which could be used to induce anaesthesia and which could possibly be given intermittently or by infusion for maintenance. There were a number of easily identifiable drugs such as thiopentone or methohexitone which fell into this category. Other agents such as diazepam could be given to produce a light level of sedation or basal narcosis in larger doses, but there was no suggestion that they would replace the conventional drugs.

In the past few years this distinction has become less clear—probably starting with the "neurolept" drugs. This combination of a potent analgesic and a neuroleptic or sedative drug is being used to induce anaesthesia and the 1977 index of *Anesthesiology* lists one of the constituents—droperidol—under i.v. anaesthesia. In addition, the preliminary administration of fentanyl or other potent analgesics has made "induction" possible with what would normally be sub-hypnotic doses of induction agents. By reducing the frequency of muscle movement it has also made the use of drugs such as etomidate acceptable for induction of anaesthesia. Thus we now have the "traditional" i.v. anaesthetics and a variety of drug combinations which can be used to induce anaesthesia. Strictly speaking, the latter are outside the scope of this paper, but it would be foolhardy to ignore combinations which are becoming increasingly popular in anaesthesia.

CLASSIFICATION AND AVAILABLE DRUGS

I.v. anaesthetics can be classified according to their chemistry, their speed of onset of action or their clinical acceptability. A classification based on the duration of action is unsatisfactory, although this is important in relation to the fields of usefulness of individual agents. The terms "ultra-short" and "short" acting are often used indiscriminately and can be both confusing and misleading to those who are unaware of the pharmacokinetics of these drugs. Table I is based on their speed of onset and their chemistry. When an i.v. anaesthetic drug is to be given intermittently to maintain a desired level of anaesthesia it is important that it should produce its desired effect in one arm–brain circulation time; thus fluctuations of depth will be minimal. This is less important when it is used primarily for induction, although it is desirable, particularly in patients who were either unusually sensitive or resistant to anaesthetics. Rapidly acting drugs will, in effective doses, produce loss of consciousness in one arm–brain circulation time.

TABLE I. *Classification of intravenous anaesthetics*

Rapidly acting (induction agents)
- Thiobarbiturates, methylbarbiturates
- Eugenols
- Steroids
- Imidazole derivatives
- Di-isopropyl phenol

Slower acting (basal hypnotics; sedatives)
- Phenyl cyclohexamines
- Benzodiazepines
- Opiate–neuroleptic/tranquillizer combination
- Large doses of opiates

The rapidly acting drugs are primarily induction agents which can also be used for maintenance of anaesthesia, either alone or preferably with an analgesic (parenteral or inhalation of nitrous oxide and oxygen). Within this group, the rapidly metabolized eugenols could justifiably be termed ultra-short acting and the alphaxalone–alphadolone mixture (Althesin) which depends on both translocation and detoxication for recovery could be referred to as "short" acting. When given by intermittent administration or by infusion these will have a less cumulative effect than the barbiturates. The position of the imidazole derivative, etomidate (Hypnomidate), is not clear with respect to recovery, as one usually has to give it with an analgesic to produce acceptable anaesthesia and this affects recovery.

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Generally speaking, drugs which have a rapid onset of action will act for a shorter time than more slowly acting compounds. This also applies to the i.v. anaesthetics. In normal induction doses, diazepam and the neurolept drugs are much longer acting than thiopentone or Althesin. However, by virtue of this it is easier to use the longer-acting drugs or basal narcotics or to produce a light level of sedation.

As an extension of table I, many of these drug groups could be classed as acceptable or unacceptable. With increasing competition from new drugs many of the unacceptable ones have been withdrawn from clinical use. As an example the barbiturates have been classed as:

Very satisfactory and equally acceptable	Thiopentone, thiamylal, thiobutobarbitone and thialbarbitone
Unsatisfactory with an unacceptably high frequency of side-effects	Hexobarbitone, methitural, buthalitone
Unique advantages but some side-effects	Methohexitone and enibomal

All of the second group have now been withdrawn from clinical use.

Likewise the early eugenols, G 29505 and Propinal have been replaced by propanidid (Epontol). The first steroid to be used clinically—hydroxydione—was abandoned because of venous thrombosis and very slow onset of action, but its successor Althesin is rapidly acting. It too may be abandoned because of a high frequency of hypersensitivity reactions and it is likely that a water-soluble steroid (minaxolone) will prove suitable for clinical use.

The first of the phenyl cyclohexamine compounds, phencyclidine, is no longer used clinically because of prolonged side-effects. This also applies to cyclohexamine, and ketamine is the only drug of this series in clinical use. The benzodiazepine tranquillizers which are used for induction of anaesthesia must have a fairly short onset time. This is acceptable (1–2 min) in the case of diazepam and flunitrazepam but not with lorazepam (20–40 min), which is not suitable for use as an i.v. anaesthetic. The new, water-soluble midazolam has a slightly shorter onset time and may well replace the older drugs, by virtue of lower frequency of injection pain and post-injection phlebitis and thrombosis.

This survey is limited to etomidate, minaxolone (the new steroid), ICI 35868 and midazolam (the water-soluble benzodiazepine).

ETOMIDATE

Known also as R 26490 this hypnotic, which was synthesized in the Belgium laboratories of Janssen Pharmaceuticals, is chemically unrelated to any commercially available anaesthetic (fig. 1). It has recently been released for clinical use under the trade name Hypnomidate. Although it is soluble in water, the resultant solution is unstable and causes pain on injection and the commercially available preparation contains 2 $\mu g\ ml^{-1}$ in propylene glycol. There is no problem with the stability of this preparation, which can be left at room temperature for more than 2 years.

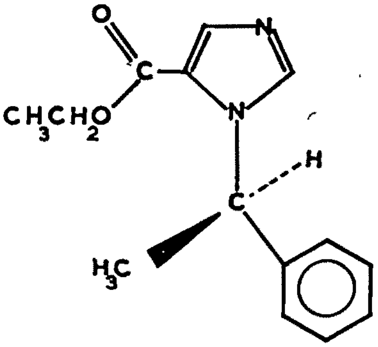

FIG. 1. Formula of etomidate.

Pain on injection is one of the problems with the direct i.v. injection of etomidate. It is most common when injections are made into small veins on the back of the hand, when there is a frequency of about 50% (Dundee and Zacharias, 1979).

Etomidate is definitely a rapidly acting drug, with effective doses causing loss of consciousness in one arm–brain circulation time. It is approximately 12 times more potent than thiopentone.

Van Hamme, Ghoneim and Ambre (1978) have studied the pharmacokinetics of etomidate. Plasma concentrations following administration of 0.3 mg kg^{-1} follow a tri-exponential pattern. The mean half-life for the first phase was 2.6 ± 1.3 min, for the intermediate phase was 28.7 ± 14.0 min and final $T_{\frac{1}{2}}$ for elimination was 4.6 ± 2.6 h. There is a very large apparent volume of distribution which indicates considerable tissue uptake. The hepatic clearance, being about 50% of hepatic blood flow, indicates that changes in hepatic blood flow or metabolism in the liver will only have moderate effects on the disposition of etomidate in the body.

Etomidate is heavily bound (78%) to plasma albumin. Renal excretion accounts for 87% of the injected drug (3% unchanged) with 13% in the bile (Heykants et al., 1975).

Recovery from a single dose is quick, being intermediate between that of equivalent doses of thiopentone and methohexitone. On repeated administration, etomidate is less cumulative than any of the available barbiturates.

The frequent occurrence of extraneous muscle movement in unpremedicated patients is a major disadvantage of etomidate, but there is a great lack of uniformity in the frequency of reporting of this complication. The frequency is reduced dramatically by premedication with diazepam, and even more markedly by opiates (Dundee and Zacharias, 1979). The practice of giving i.v. fentanyl immediately before etomidate is the most likely explanation for the failure of many workers to consider excitatory side-effects as a main disadvantage of etomidate. Our findings with a fixed dose (0.3 mg kg^{-1}) of etomidate and various premedicants are given in table II, and show the protective action of fentanyl. Regrettably, the prior use of fentanyl is followed by too great a frequency of vomiting to make this combination suitable for minor procedures especially in outpatients.

TABLE II. *Percentage frequency of excitatory effects when etomidate is injected at two speeds with the premedicants shown. Etomidate was given in doses of* 0.3 *mg* kg^{-1} *of the propylene glycol formulation.* (*Twenty patients in each series*)

Premedicant	Speed of injection 1 mg s^{-1}	 2 mg s^{-1}
Nil	85	95
Diazepam 10 mg	85	75
Pethidine 75 mg	25	30
Fentanyl 50 μg	75	60
Fentanyl 100 μg	20	60
Droperidol + fentanyl	55	55
Papaveretum 20 mg + hyoscine 0.4 mg	40	40

In unpremedicated patients, induction doses of etomidate are followed by a frequency of cough or hiccup, or both, similar to that seen with methohexitone. Although they occur more frequently than with thiopentone, these respiratory complications are not severe and rarely interfere with the course of anaesthesia. There appears to be some relationship between the occurrence of excitatory effects and respiratory complications and perhaps movements of the diaphragm may be a common factor. This view is supported by the fact that premedication with pethidine reduces both muscle movements and respiratory upset.

In the early studies Kettler and colleagues (1974) found that etomidate had minimal effects on the cardiovascular system and this has been one of the features of most of the clinical reports of this drug. In fact, it is this lack of cardiovascular depression which has led to its continuing use despite the undesirable features. Dundee and Zacharias (1979) have reviewed the published papers on this aspect of etomidate, and these confirm its lack of direct cardiovascular toxicity, slight hypotensive action and slight decrease in peripheral resistance and a decrease in coronary resistance.

Unlike many other i.v. anaesthetics no increase in circulatory histamine following etomidate could be demonstrated by Doenicke and colleagues (1973). Rashes are not common after its use and in our series we found this on three occasions in 1400 administrations. In the light of the increasing frequency of hypersensitivity reactions with i.v. anaesthetics, this absence of histamine release is a major point in favour of etomidate.

Unpublished data on liver function studies with intermittent doses for minor procedures or with infusions for the intermediate type of operations have revealed no abnormality. On the debit side, venous thrombosis has proved troublesome with each of the available preparations, occurring in about 16% of patients with Hypnomidate 0.3 mg kg^{-1}. This is definitely greater than with methohexitone or thiopentone. The propylene glycol solvent form of etomidate caused a greater frequency of venous sequelae than did the aqueous or polyethylene glycol preparation (Zacharias et al., 1979).

MINAXOLONE (CCI 12923)

This water-soluble steroid was developed at the Glaxo-Allenbury Research Laboratories, following their earlier experiences with alphaxalone-alphadolone acetate (Althesin). It was generally agreed that the need for a solubilizing agent made Althesin a less desirable induction agent than it might otherwise have been, as well as having possibly contributed to the high frequency of hypersensitivity reactions.

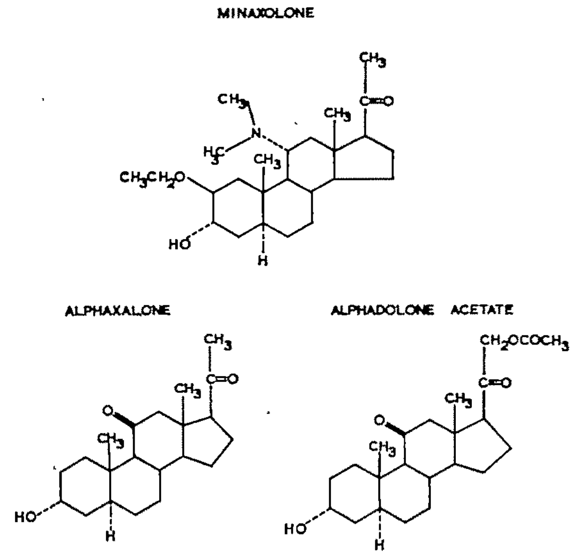

FIG. 2. Formulae of minaxolone, alphaxalone and alphadolone acetate.

Figure 2 gives the formulae for minaxolone (2β - ethoxy - 3α - hydroxy - 11α - dimethylamino -5α-pregnan-20-one) and compares it with the constituents of Althesin. The preparation, which was released for clinical trials towards the end of 1978, contains 5 mg of steroid per millilitre. It is dissolved in an aqueous solution of sodium citrate and sodium chloride with a pH of 4.0 unit.

Its anaesthetic properties have been studied in a number of animals, and these show that minaxolone has about three times the potency of Althesin (Davis et al., 1979). Induction was rapid in all species studied, with loss of consciousness occurring within 10–15 s of injection. Recovery times appeared to be similar to those for equivalent doses of Althesin. On repeated injection it had a cumulative effect similar to that of Althesin and much less than thiopentone. Minaxolone was effective when given i.m. to monkeys, the induction time being 4 min. Surgical anaesthesia was also maintained by continuous i.v. infusion for periods up to 6 h. There was no obvious incompatibility between minaxolone and other drugs used during anaesthesia. In addition to the anaesthetic effects, minaxolone has an anticonvulsant action. It resembles thiopentone in having no analgesic action in small doses.

In initially conscious unrestrained cats, equivalent doses of minaxolone, Althesin and thiopentone caused immediate decreases in arterial pressure which were greatest with thiopentone and least with minaxolone. These initial decreases were accompanied by transient tachycardia, but the heart rates then decreased to less than the control values. The transient arterial pressure decrease was followed by a "rebound" increase, the arterial pressure then decreased to about 20% less than control and remained at this value during the period of anaesthesia. In cats and dogs neither steroid anaesthetic caused the marked respiratory depression seen with thiopentone.

Minaxolone has a weak antispasmodic action on the isolated gut. Only unacceptably great concentrations reduce the tone or inhibit spontaneous contractions of the isolated jejunum.

Tests for hormonal activity following i.v. minaxolone have failed to reveal any mineralocorticoid, glucocorticoid, androgenic, oestrogenic, anabolic, antigonadotropic or progestational effects.

The pharmacokinetics of minaxolone are not yet known in detail. It is metabolized and excreted via the bile and urine. The mean half-life of unchanged drug in the plasma was 40 min in the rat and 43 min in the cat. Repeated daily injections in rats and dogs showed no difference in the profile of plasma concentrations, suggesting that neither accumulation nor enzyme induction significantly affect plasma concentration. Minaxolone rapidly crosses the placenta and it is widely distributed in the fetus.

Long-term and high-dose administration of minaxolone have failed to reveal any disturbing toxic effects. Likewise, its effect on intra-arterial injection is minimal and less than that of thiopentone. When 0.5 ml of 0.5% minaxolone was injected into the central artery of a rat ear, the effects (like those of Althesin) were attributable to mechanical injury, whereas thiopentone produced some areas of epidermal necrosis. These findings suggest that it is unlikely that the accidental intra-arterial injection of minaxolone in man will cause the same severe tissue damage as sometimes follows the intra-arterial injection of thiopentone.

Clinical effects

Preliminary results were presented at a meeting of the Anaesthetic Research Society in March 1979 (Aveling et al., 1979). At the time of writing, minaxolone is still at an early stage in its clinical trials. It has been given to more than 100 patients by the author and two colleagues (R. S. J. Clarke and H. G. McNeill) and our findings are summarized here.

Minaxolone is easy and painless to inject. A follow-up for 14 days has not shown any venous thrombosis. It is definitely a rapidly-acting drug. The rapid injection of 0.5 mg kg^{-1} into a large forearm vein following a period of reactive hyperaemia, as described by Clarke and colleagues (1968), resulted in sleep occurring in between 8 and 13 s (average 10.25 ± 0.53 s) in 11 patients. These times are within the normal limits of the arm–brain circulation.

The induction dose is in the region of 0.5 mg kg^{-1} although consciousness is usually lost with 0.3 mg kg^{-1}. In unpremedicated subjects there is a tendency for slight hypertonus, but this has not upset the course of anaesthesia. Further supplements are required for procedures lasting longer than 3–4 min and a total dose of 1.5 mg kg^{-1} has been given. There have been no problems with the uptake of volatile and gaseous anaesthetic following minaxolone, but it may prolong the action of suxamethonium.

Following normal induction doses, recovery has been prompt but, with intermittent injection, it would appear to have a duration of action similar to, or perhaps slightly longer than, Althesin.

Hypotension, tachycardia and respiratory depression have not been features of its use.

Our experience suggests that minaxolone is a most promising induction agent, well worthy of further study.

ICI 35868

This has a simple chemical structure (fig. 3)—2,6-di-isopropyl phenol—which is unrelated to any other i.v. anaesthetic. It has a low water solubility and is prepared for i.v. injection in a solution containing ICI 35868 10 mg ml^{-1} in 16% Cremophor EL. The solutions used in some of the early clinical studies reported by Kay and Rolly (1977a, b) also contained 8% ethyl alcohol. Details of its clinical pharmacology have not been published and the following data were supplied by J. B. Glen. At the time of working there are only two publications on its use (Kay and Rolly, 1977a, b).

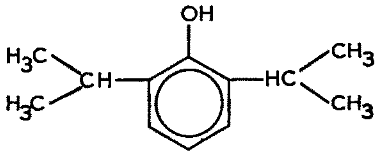

FIG. 3. Formula of ICI 35868.

The anaesthetic activity of ICI 35868 has been demonstrated in the mouse, rat, rabbit, frog and rhesus monkey and it appears to be a short-acting agent with a potency similar to that of methohexitone. Experiments in mice show that the rate of onset of anaesthesia is rapid and the cumulative effect of the agent on repeated injection is insignificant when compared with thiopentone sodium. Recovery from anaesthesia with ICI 35868 is rapid and free from excitatory side-effects.

The electroencephalographic changes induced by ICI 35868 in the rat were similar to those seen with standard i.v. agents in this species and burst suppression was produced by a dose close to the median hypnotic dose.

In studies in conscious pigs haemodynamic and respiratory changes were similar to those produced in pigs with equivalent doses of thiopentone or Althesin. No changes in bronchomotor tone were detected following the administration of ICI 35868 to pigs anaesthetized with pentobarbitone. During the maintenance of anaesthesia with an infusion of ICI 35868 in pigs, the pressor responses obtained on administration of adrenaline and noradrenaline were greater than those obtained from the same animals in the conscious state. The response to acetylcholine was similar in both situations.

Experiments in cats indicate that lethal doses of ICI 35868 produce respiratory arrest before cardiac failure. When ventilation is supported, larger doses of ICI 35868 are tolerated. In common with thiopentone and Althesin, ICI 35868 produced dose-related decreases in pressure in an isolated perfused hind limb preparation, indicating that at least a portion of the hypotensive effect of these agents is the result of a decrease in peripheral vascular resistance.

ICI 35868 does not have a topical local anaesthetic effect when applied to the rabbit cornea.

In man, chlorpromazine, diazepam and large doses of amylobarbitone significantly increase the sleeping time produced by ICI 35868. In experiments to study the combination of ICI 35868 with inhalation agents and commonly used neuromuscular blocking drugs, no unexpected interactions were observed.

Anaesthesia has been maintained in rats, cats and pigs with ICI 35868 given by intermittent injection or by infusion, for periods up to 5 h.

Kay and Rolly (1977a) have reported the administration of ICI 35868 to human volunteers and patients. Doses of 0.2 mg kg^{-1} of ^{14}C-labelled drug showed a plasma half-life of 30 min. Only 10% of the drug was not metabolized. Elimination from the body was rapid, 80% of the administered dose being excreted in the urine within 24 h—almost entirely as a single metabolite. A study in 22 unpremedicated subjects, in whom the drug was injected, showed the induction dose to be in the region of 1 mg kg^{-1}. There were no complications during induction and the only side-effect was pain at the site of infusion in five subjects. There was no apparent correlation between the rate of injection and the dose required to produce sleep. Cardiovascular and respiratory effects were minimal. Further studies in premedicated subjects show that the drug is rapidly acting, with average onset time of 30 s. Again, pain on injection was the only notable complication.

Other studies showed a transient dose-related respiratory depression which was less than that caused by the equivalent dose of methohexitone. Perhaps the most important investigation was that of the duration of action following incremental doses. There was little evidence of a cumulative effect and total doses of 3–22 mg kg^{-1} show no evidence of toxicity.

The rapidity of onset, smooth induction and lack of cumulation from repeated doses would seem to be advantages of ICI 35868. On the debit side there is the need for a solubilizing agent and consequent fear of hypersensitivity reactions and pain on injection. The removal of alcohol from the formulation may reduce the latter (Kay and Rolly, 1977b). The fact that it appears to be free from the excitatory effects of some barbiturates and the steroids would suggest that it is worthy of further study.

MIDAZOLAM MALEATE

The frequency of pain on injection and postoperative venous thrombosis with diazepam was such as to stimulate a search for less irritant compounds. Flunitrazepam had many advantages in this respect, but it is not freely available for clinical use. More recently midazolam (Ro 21–3981), a water-soluble benzodiazepine, has been introduced and is currently undergoing clinical trials in America.

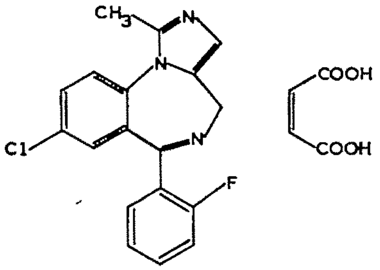

FIG. 4. Formula of midazolam maleate.

Figure 4 gives the chemical formula of midazolam maleate. This compound exhibits a pH-dependent ring-opening phenomenon in which the benzodiazepine ring closes at pH greater than 4.0, but opens reversibly at pH values less than 4.0 (fig. 5). The compound is stable in aqueous solution and highly water soluble, but the solubility is pH-dependent (approx. 85 mg ml^{-1} at pH 2.7 and 0.3 mg ml^{-1} at pH 7.6). The material available for clinical trial is a buffered aqueous solution containing 2.5 mg ml^{-1} at pH 3.5. The physiological pH maintains the closed ring and enhances the lipoid solubility of the drug and this contributes to the speed of onset of activity after i.v. administration.

Midazolam has been extensively studied in animals (Midazolam Maleate, 1979). Like diazepam, it causes a dose-related depression of the central nervous system, varying from behavioural changes to

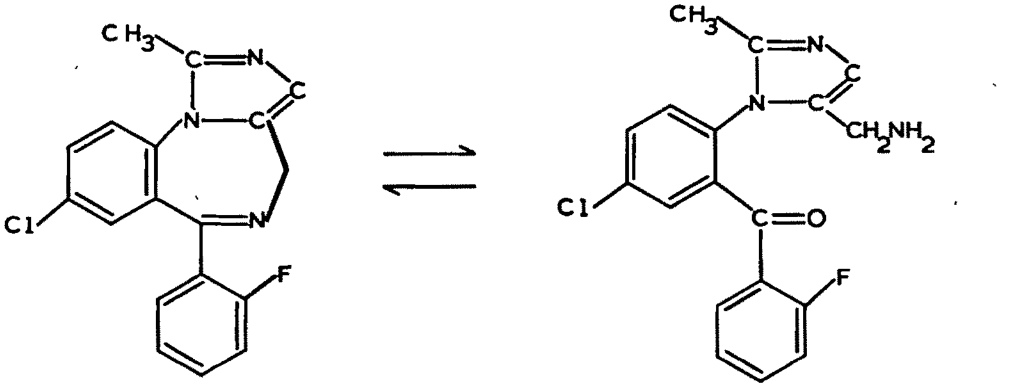

FIG. 5. Formula of pH-dependent ring opening of midazolam. The benzodiazepine ring closes at pH greater than 4.0 unit, but opens reversibly at pH less than 4.0.

sedation and sleep. It also has anticonvulsant activity qualitatively similar to that of diazepam. Like diazepam, midazolam has no direct effect on neuromuscular transmission and does not affect the action of myoneural blocking drugs. Both benzodiazepines increase the amplitude and duration of the dorsal root potential in the spinal cat, indicating an enhancement of presynaptic transmission; this effect is produced by a mechanism which involves gamma-aminobutyric acid (GABA). Midazolam would appear to be twice as potent as diazepam in its action on the nervous system, but its duration of action is less.

In i.v. doses of 1–10 mg kg^{-1}, midazolam has little effect on the cardiovascular system in the dog. In other studies there was a dose-dependent decrease in arterial pressure with doses of 0.25, 1.0 and 10.0 mg kg^{-1}, with no effect on heart rate or cardiac output. However, doses of 1 or 10 mg kg^{-1} resulted in a significant decrease in right ventricular and septal coronary blood flow, this being opposite to the effect of diazepam, which slightly increased coronary blood flow.

Midazolam caused no notable effect on gastrointestinal activity, nor did it affect histamine-induced bronchoconstriction. However, slight increases in airway resistance occurred at some doses. A similar effect has been noted with diazepam (Dalen et al., 1969).

A battery of acute and chronic toxicity studies, carried out in several animals, have shown no ill-effects attributable to midazolam. Likewise, it has no effect on the reproductive process and no teratogenic action.

Midazolam is converted to the 1-hydroxymethyl (Ro 21-6347) and 4-hydroxy metabolite (Ro 21-5975) in the mouse; these appear in the plasma within 5–20 min of i.v. administration. The 4-hydroxy metabolite concentration increases 5–10 times less than that of the 1-hydroxymethyl, but neither contributes to the soporific action of the midazolam. Studies of plasma concentrations in man and animals show an initial rapid redistribution and give a tri-exponential curve, which could be fitted to a three-compartment model with elimination from the central compartment. The apparent elimination half-life was 45–120 min in dogs, while the terminal half-life was between 1.3 and 2.2 h in man. This suggests that the drug would not accumulate to any appreciable degree during chronic administration.

In midazolam concentrations of 1, 5 and 10 μg ml^{-1}, the binding of the drug to human plasma protein is in excess of 95% as estimated by equilibrium dialysis. This may contribute to the great individual variation in response which will be discussed later.

The animal studies point to a promising new, safe water-soluble benzodiazepine. The author and colleagues have given doses varying from 5 to 25 mg to about 50 subjects and our findings will be reviewed with published papers on midazolam.

One is immediately impressed by the lack of viscosity of midazolam compared with diazepam. There is no pain on injection, even in small veins. A detailed follow-up, for up to 14 days after injection, has not revealed any residual thrombosis. This is in keeping with the animal studies of Pagano and colleagues (1978) who found no histological evidence of vascular pathology in the veins of rats 48 h after injection of midazolam.

Like other injectable benzodiazepines, midazolam produces a dose-related cerebral depression with tranquillization, sedation, drowsiness and sleep occurring with increasing dosage. However, like diazepam and flunitrazepam there is a great individual variation in response to midazolam. This variation is not so important when it is used for "instant premedication", or for sedation as, for example, during dental anaesthesia. It places limits on its use as an induction agent, when one may also have to use small doses of thiopentone. This variation in response has also been noted by Conner and colleagues (1978)

It is difficult to assess the onset time with drugs such as benzodiazepines, but clinical impressions suggest that it is slightly quicker in action than diazepam. The maximum effect usually occurs in 80–90 s after injection of an effective dose; that is in agreement with the findings of Reves, Corssen and Holcomb (1978).

Likewise it is difficult to assess the relative potency of diazepam and midazolam. Reves, Corssen and Holcomb (1978) found that diazepam 0.3 mg kg^{-1} and midazolam 0.2 mg kg^{-1} were necessary to produce sleep in at least 90% of patients and on this basis they concluded that midazolam is one-and-a-half times as potent as diazepam. The writer feels that the ratio is nearer 2 : 1.

Difficulty exists in assessing the relative duration of action of the benzodiazepines. The author agrees with Reves, Corssen and Holcomb (1978) that it is shorter acting than equivalent doses of diazepam. A 70-kg anaesthetist was fully awake 2½ h after midazolam 10 mg and able to do an afternoon's work. In four volunteers no midazolam was found in the plasma 8 h after administration of 5 mg and this differs markedly from the findings with diazepam. Table III gives the duration of effect in four male subjects (average age 34 yr; average weight 72 kg) each of whom received midazolam 5 and 10 mg at an interval of 14–16 days.

TABLE III. *Duration of various facets of drug action in four subjects, each of whom received two doses of midazolam at intervals of at least 14 days*

	Average time (min) to		
Dose of midazolam	Respond to command	"Peg board" test return to normal	Fully awake and mobile
5 mg	7	42	67
10 mg	18.5	119	121

Conner and colleagues (1978) found a degree of anterograde amnesia following midazolam 5 mg comparable to that observed with diazepam 10 mg. We have observed amnesia for about 1 h after apparently full recovery from midazolam 10 mg.

All the reported studies agree with our experience of lack of cardiovascular toxicity of clinical doses of midazolam. Short periods of apnoea have been noted when the full c.n.s.-depressant effect has occurred, but these were of no clinical significance.

In the light of the extremely high frequency of pain on injection and venous thrombosis with injectable diazepam (Hegarty and Dundee, 1977), midazolam would appear to offer many advantages over available benzodiazepines and it seems worthy of further study.

ACKNOWLEDGEMENTS

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INOTROPIC AGENTS

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Selection of drugs to support the failing circulation is a fashionable topic: a review of selected journals over the past 5 years resulted in the collection of more than 250 references. It is easy to be bewildered by so much information and before discussing individual drugs it is worth considering why some of the conclusions appear to provide conflicting advice.

The performance of the normal heart is governed by a number of intrinsic and extrinsic regulatory mechanisms which are integrated with the peripheral circulation. Drugs can affect the system by acting directly on the myocardium, by influencing the autonomic nervous system or by altering the peripheral circulation, and any changes which occur are influenced to some extent by the conditions of the study.

Experimental work is often undertaken using isolated intact hearts (Serur and Urschel, 1973), papillary muscles (Huntsman and Stewart, 1977) or myocardial strips (Lumley, Broadley and Levy, 1977), usually obtained from healthy animals. Such preparations provide well-controlled conditions for examining drug effects on myocardial fibres, but the results are not always applicable clinically because the design of the study excludes consideration of reflex responses evoked *in vivo*, or the influence of disease, and only rarely allows for species variation (Prasad, 1975). Experiments on isolated human papillary muscle removed at surgery (Prasad, 1972) avoid some of these limitations, but here again, effects demonstrated *in vitro* do not necessarily occur *in vivo* and there are only a limited number of conditions which permit operative removal of large pieces of myocardium.

Experiments on intact animals reveal the influence of drugs on the integrated circulation, but procedures designed as a model for human disease are often a poor replica, for example embolization or ligation of a coronary artery in a previously healthy dog differs from the intermittent ischaemia with increased left ventricular end-diastolic pressure and localized dyskinesia which so commonly precedes complete occlusion of a coronary artery in man. Another difficulty is that some experiments on intact animals involve sites of drug administration or dose regimes which are inapplicable as a therapeutic schedule, for example drug administration directly into the coronary arteries (Liedtke et al., 1972), or drugs infused in massive doses (Banka et al., 1975).

Many of these limitations are avoided by investigating the actions of drugs in man, but this raises ethical constraints and often an inability to control more than one or two of many closely related variables. A rather more insidious problem is encountered when the results of investigations which can be carried out with relative ease on mildly abnormal subjects are applied to the grossly abnormal individual in whom accurate haemodynamic measurements are so difficult to make.

As myocardial function deteriorates, changes in pre-load exert less and less effect on either stroke volume or stroke work until eventually stroke volume is independent of filling pressure and stroke work may even decrease as the filling pressure increases (Bradley, 1977). At the same time, the failing heart loses its ability to respond to inotropic agents so that any effect derived from the drug will be governed by its other properties such as its action on heart rate or on peripheral resistance (Gunnar et al., 1967; Serur and Urschel, 1973).

Similarly, the results of decreasing after-load will change both as heart failure worsens and as filling pressures increase. The normal heart responds to an increase in after-load by contracting more powerfully so that, at a constant filling pressure, stroke work increases but stroke volume remains unchanged. As the heart fails, this mechanism fails too and an increase in after-load leads to a decrease in stroke volume (Ross and Braunwald, 1964). Conversely, as the after-load is decreased, stroke volume will increase even though stroke work is unchanged. If, however, the decrease in afterload is accompanied by a massive decrease in pre-load (i.e. filling pressure), both stroke volume and stroke work may decrease, although this becomes less likely as cardiac failure worsens (fig. 1).

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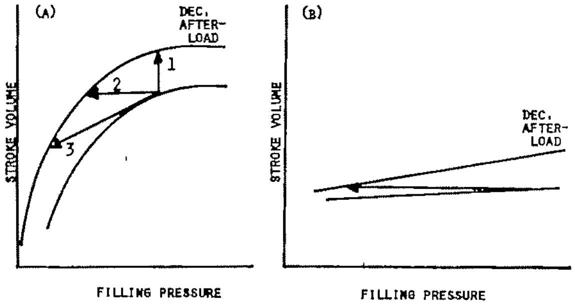

FIG. 1. The effect on stroke volume of reducing after-load, (A) when the heart is relatively normal; (B) when heart failure is severe. 1 = filling pressure unchanged; 2 = moderate decrease in filling pressure; 3 = profound decrease in filling pressure.

Another factor which must be considered is that some myocardial injuries, especially those caused by ischaemia, are focal rather than global, and the response to a drug in the damaged area may differ from that seen in the surrounding normal tissue (Moore and Parratt, 1973). In this context the behaviour of the coronary circulation is particularly important because, if there is extensive coronary arterial disease, unpredictable effects will occur if some areas of the myocardium respond to a drug whereas others do not, while some parts of the coronary circulation can dilate but others are fixed (Buckberg and Ross, 1973; Dumesnil et al., 1975). Evaluating drug responses under such circumstances is particularly difficult because overall haemodynamic effects and global indices of myocardial oxygenation, such as coronary sinus oxygen or lactate content, provide little information about regional changes (Crexells, Bourassa and Biron, 1973), and simple indices such as the extent of ST elevation can be misleading (Becker, Ferreira and Thomas, 1975; Norris et al., 1975). The development of echocardiographic and nuclear imaging techniques provides some optimism for more accurate assessment in the future (Holman et al., 1974; Gibson, 1975).

Two final points must be borne in mind. The first is that the cardiac sequelae of prolonged haemorrhagic hypotension, septicaemia, cardiopulmonary bypass, myocardial infarction and chronic cardiac failure from any cause differ enormously, even though all can produce a clinical picture of the "low output state". Second, drug effects can be modified by other features of the patient's condition, for example increased concentrations of endogenous catecholamines or other pressor agents (Taylor et al., 1977), depletion of local stores of noradrenaline (Dequattro et al., 1973), biochemical derangements such as hypoxaemia, hypokalaemia or acidosis (Darby et al., 1960), synergistic or conflicting effects from other drug treatment (Falicov et al., 1973; Guideri, Barletta and Lehr, 1974), and abnormal pharmacokinetics secondary to impaired tissue perfusion (Aps et al., 1976). All these factors influence not only the interpretation of haemodynamic studies but also the selection of drug treatment on an individual basis.

Catecholamines

Six drugs fall into this category: adrenaline, noradrenaline, isoprenaline, dopamine, dobutamine and salbutamol. Their pharmacological properties have been reviewed by Gibson and Coltart (1971), Rosenblum (1974), Ahlquist (1976a, b), Goldberg, Hsieh and Resnekov (1977) and Leier, Webel and Bush (1977). All stimulate the myocardium directly, but to very different degrees. Isoprenaline, dobutamine and adrenaline are powerful, dopamine has moderate inotropic properties which are apparent at doses greater than 5 μg kg^{-1} min^{-1} (Beregovich et al., 1974; Goldberg, 1974), noradrenaline is less than 5% as effective as isoprenaline, and salbutamol is very weak (less than 0.1% as effective as isoprenaline) although its action is more prolonged (Poole-Wilson et al., 1977). The action of dopamine is unusual in that it is mediated in part by stimulating local release of noradrenaline (Goldberg, 1972). When tissue stores are depleted as in chronic congestive cardiac failure (Chidsey et al., 1963) or following cardiopulmonary bypass (Lewis et al., 1978), its effects may be less than anticipated or its vasoconstrictor properties may become more obtrusive.

All the catecholamines have chronotropic properties too, prominent with isoprenaline, adrenaline and salbutamol, but less marked with dobutamine and dopamine (Beregovich et al., 1975; Lumley, Broadley and Levy, 1977; Stoner, Bolen and Harrison, 1977). Noradrenaline injected i.v. usually causes a bradycardia secondary to vasoconstriction.

Both the chronotropic and inotropic properties of these drugs are antagonized by beta-adrenergic blocking agents. Massive doses of the agonist can still evoke a myocardial response, but this means that any unblocked actions of the drug on the peripheral circulation will be exaggerated (Conolly, Kersting and Dollery, 1976).

The effects of the catecholamines on the peripheral circulation differ considerably. Noradrenaline is a powerful vasoconstrictor, adrenaline has both vasoconstrictor and vasodilator effects, whereas isoprenaline has only vasodilator properties. Salbutamol, a selective beta-2-agonist, is less powerful than isoprenaline, but the difference in potency is much greater for the cardiac than the peripheral effects (1 : 2000 cardiac; 1 : 10 peripheral). Dopamine is unique in that, at small doses (0.5–5.0 μg kg^{-1} min^{-1}), it selectively dilates renal (McDonald et al., 1964) and mesenteric vessels (Shanbour and Parker, 1972), probably by stimulating dopaminergic receptors there. At greater doses (more than 20 μg kg^{-1} min^{-1}) it has vasoconstrictor effects (Goldberg, 1974). Dobutamine has only minimal effects on the peripheral circulation (Robie and Goldberg, 1975; Berkowitz et al., 1977), some of which probably represent a reflex response to the increase in cardiac output which occurs because of its inotropic action (Loeb, Bredakis and Gunnar, 1977). The effects of these drugs on some important vascular beds are summarized in table I.

It is essential to note that these are the findings in *normal* subjects. When the cardiac output or arterial pressure is low, any agent which increases the output or increases the pressure will increase flow, at least to the brain, heart and kidneys. Long-term benefit will follow only if the increased perfusion of vital structures leads to progressive improvement in their function with subsequent return of flow to inessential tissues as well. Whether or not this occurs depends in many cases on whether or not the myocardium can sustain an adequate work load and is supplied with sufficient oxygen (Sonnenblick, Ross and Braunwald, 1968; Braunwald, 1971; Lesch, 1976). Factors which increase myocardial oxygen requirements are increases in heart rate and in force of contraction, particularly with generation of increased systolic pressures. The normal coronary circulation dilates in response to an increased oxygen demand and this reflex response takes precedence over the direct effects of agents such as noradrenaline, adrenaline and dopamine which are coronary vasoconstrictors, unlike isoprenaline and salbutamol which dilate coronary vessels directly (Rosenblum, 1974; Ross, 1974). When the coronary circulation is abnormal, reflex increases in blood flow may not be possible and the effects of drugs differ, both on overall coronary flow and on its distribution within the myocardium (Meyer et al., 1976; McClenathan et al., 1977). The balance between myocardial oxygen requirements and availability can be altered adversely, so causing or worsening myocardial ischaemia. This is particularly likely to occur with isoprenaline because it has the most powerful cardiac stimulant effect, with tachycardia a prominent feature (Buckberg and Ross, 1973; Winsor and Wright, 1975). However, it must be remembered that if the heart rate is already increased, then a sympathomimetic agent which improves cardiac output and restores tissue perfusion can cause a *decrease* in heart rate.

Vasodilators

The deleterious effects of excessive vasoconstriction have been recognized for more than 50 years (Erlanger, Gesell and Gasser, 1919) and vasodilator therapy has been advocated sporadically for at least 15 years (Lillehei et al., 1964). Several groups of drugs have been used:

Alpha-adrenergic blocking agents	phentolamine* chlorpromazine
ganglionic blocking agents	hexamethonium trimetaphan
direct vasodilators	
acting mainly on arterioles	hydrallazine
acting on both arterioles and venules	sodium nitroprusside
acting mainly on venules	glyceryl trinitrate isosorbide dinitrate
beta-2 sympathomimetic agonists	salbutamol

(* complex effect—see text).

The properties of alpha-adrenergic blocking agents and ganglionic blocking drugs are too well known to warrant reiteration here and, with the exception of phentolamine, they are used only occasionally in the treatment of acute or chronic circulatory insufficiency

TABLE I. *Effects of some catecholamines on blood flow in peripheral vascular beds. *High doses of dopamine constrict renal and mesenteric vessels*

	Coronary	Renal	Mesenteric	Skin/muscles
Adrenaline	Increase	Decrease	Decrease	Decrease
Noradrenaline	Increase	Decrease	Decrease	Decrease
Isoprenaline	Increase	No change	Increase	Increase
Dopamine	Increase	Increase*	Increase*	Decrease
Dobutamine	Increase	No change	No change	Increase
Salbutamol	Increase	?(No change)	?(No change)	Increase

(Stinson et al., 1975; Nitter-Hauge, 1978). Phentolamine (Gould and Reddy, 1976) is unusual in that it appears to act as an alpha-adrenergic blocking agent, a beta-agonist, has a direct dilator effect on vascular smooth muscle and causes the release or increased synthesis of local stores of noradrenaline. In spite of this complex action, the effects of i.v. phentolamine resemble those of sodium nitroprusside, with the important exception that phentolamine causes tachycardia whereas nitroprusside rarely does when given to improve circulatory failure.

Sodium nitroprusside dilates smooth muscle in both arterioles and venules (Page et al., 1955), the effects being apparent within 2–5 min of starting an infusion and wearing off equally rapidly when the infusion is discontinued (Rowe and Henderson, 1974). As might be anticipated, the changes in cardiac output, coronary and renal blood flow depend on the initial conditions and the magnitude of the decrease in arterial pressure (Miller et al., 1975; Chatterjee and Parmley, 1977b; Shah, 1977; Yeh et al., 1977; Leading Article, 1978a; Mann et al., 1978). Most benefit is achieved when the drug is given to patients with increased venous pressures and a high peripheral resistance in whom a significant increase in cardiac output usually occurs with little or no change in heart rate. Both cardiac output and arterial pressure are likely to decrease if the filling pressures are normal or decreased at the outset.

The drug is difficult to handle (it is photosensitive, especially in alkaline solutions) and is metabolized to thiocyanate which can cumulate to toxic concentrations (more than 12 mg dl^{-1}) if there is renal impairment. Cyanide toxicity is not a hazard at the relatively small doses usually required for circulatory support, and tachyphylaxis is rare (Chatterjee and Parmley, 1977a; Leading Article, 1978b).

Glyceryl trinitrate can be infused (Cohn and Franciosa, 1977), applied to the skin as a cream (Armstrong et al., 1976; Parker et al., 1976; Taylor et al., 1976) or given sublingually (Dumesnil et al., 1975; Lang et al., 1976). The drug is a vasodilator acting mainly on the capacitance vessels (Chatterjee and Parmley, 1977a). This means that pre-load will decrease, but that after-load usually changes very little. As a result, cardiac output remains unchanged or may even decrease if the reduction in filling pressure is particularly marked. The heart rate tends to increase but only when the stroke volume decreases. Isosorbide dinitrate (Sweatman, Strals and Arthur, 1972; Williams et al., 1977) has been used both orally and as a sublingual preparation to achieve comparable effects over a longer time scale.

The potential benefits of vasodilator therapy can be summarized as follows:

(i) reduction of myocardial work or its redistribution so that flow increases at the expense of the generation of pressure;
(ii) reduction of myocardial oxygen requirements, either by overall decrease in myocardial work or by minimizing rate and pressure increases;
(iii) reduction in venous tone to allow redistribution of blood away from the central veins and pulmonary circulation, and so decrease ventricular end-diastolic pressure and volume when these are abnormally great, and lessen functional tricuspid and mitral valve regurgitation;
(iv) redistribution of cardiac output to essential organs and, possibly, redistribution within tissues to optimize oxygen supply at local level.

The chief hazard of vasodilator therapy is an uncontrolled decrease in arterial pressure, which means that the possibility of aggravating myocardial ischaemia must be considered, as well as any adverse effects in other vascular beds (Lesch, 1976). Three factors govern coronary blood flow: myocardial oxygen requirements, the patency of the coronary circulation and the transmyocardial perfusion pressure (aortic diastolic – ventricular diastolic pressure). If the after-load is reduced and the heart rate does not increase, myocardial oxygen requirements decrease. A reduction in aortic diastolic arterial pressure will tend to decrease coronary flow, but this may be more than compensated by the decrease in ventricular diastolic pressure or the reduced oxygen requirements. Several studies of coronary sinus flow and myocardial oxygen extraction or metabolism suggest that sodium nitroprusside, phentolamine and glyceryl trinitrate do not exaggerate myocardial ischaemia in man, in spite of their different sites of action (Gould et al., 1975; Greenberg et al., 1975; Chatterjee and Parmley, 1977b; Mann et al., 1978), and may even limit infarct size in some circumstances (Awan et al., 1976; Banka, Bodenheimer and Helfant, 1976). However, not all studies are equally reassuring, but indicate that "coronary steal" can occur (Codini, Bardfeld and Franco, 1976; Cohen, Sonnenblick and Kirk, 1976), that is that vasodilatation in healthy arteries deflects blood away from diseased vessels. These findings can but emphasize the need for better methods of monitoring regional myocardial function in man and the necessity to watch changes in pre-load and after-load with particular care when vasodilator drugs are infused. It is also worth noting that, although vasodilator therapy can improve the short-term survival of patients following myocardial infarction, the long-term results remain poor (Chatterjee et al., 1976).

Miscellaneous myocardial stimulants

Digitalis is used primarily to control supraventricular arrhythmias and its value as an inotropic agent is controversial (Schick and Scheuer, 1974; Kim, Noble and Zipes, 1975; Leading Article, 1978c). Myocardial stimulation has been demonstrated in normal subjects (Crawford et al., 1976) and in those with a variety of acute or chronic cardiac lesions (O'Rourke et al., 1976; Vatner et al., 1978), but the benefit is sometimes temporary (Cohn et al., 1975) or of questionable importance (Banka et al., 1975). All the digitalis glycosides are difficult to handle because there is a delay before peak effects are reached, even after i.v. injection, and the effects are long-lasting. It is relatively easy now to assay plasma digoxin concentrations, but unfortunately the relationship between optimum effect and plasma concentration is not clear (Leading Article, 1975; Rose, Glassman and Spencer, 1975).

Digitalis tolerance varies markedly with age (Rogers et al., 1972) and side-effects can be difficult to control. Interactions between digitalis and other factors are common (Schick and Scheuer, 1974), toxic effects being potentiated by both hypo- and hyperkalaemia, hypercalcaemia, hypomagnesaemia, hypoxaemia and alkalosis. Apart from the control of arrhythmia, digitalis is rarely indicated in acute heart failure, and prophylactic digitalization (Johnson et al., 1976) should be questioned now that drugs with simpler and more controllable effects are available. However, it is still used widely (Leading Article, 1978c), especially to treat chronic hypertensive or rheumatic heart disease.

Glucagon has both inotropic and chronotropic properties (Parmley, Glick and Sonnenblick, 1968; Murtagh et al., 1970; Smitherman, Osborn and Atkins, 1978), the chronotropic action being on the sinus node rather than on ventricular automaticity (Prasad and DeSousa, 1972). Its action is probably mediated by increasing intracellular concentrations of cyclic AMP (Afonso et al., 1972), but an inhibitory effect on membrane ATP-ase, permitting an increase in calcium influx, has also been postulated (Prasad, 1975). The effects are entirely independent of the sympathomimetic agonists and so the drug remains effective in spite of beta-adrenergic blockade (Glick et al., 1968).

Calcium is usually considered only in the context of cardiac resuscitation. The ionized fraction has transitory inotropic and peripheral vasodilator properties (Stanley et al., 1976), but only calcium chloride among the commonly used calcium salts reliably increases ionized as well as total calcium concentrations (White et al., 1976). The inotropic action is greatest when ventricular muscle fibres are shortest (Huntsman and Stewart, 1977) which may explain why synergism with adrenaline appears to occur.

Clinical considerations

Many of the drugs described in the preceding sections are widely available and have powerful and immediate effects. Inappropriate selection, or administration without adequate supervision and assessment, can be much more dangerous than withholding treatment. Hypo- or hypervolaemia, hypoxaemia, abnormalities of pH or electrolyte disturbances should always be corrected first, and monitoring the e.c.g. is mandatory if any of these drugs are to be infused i.v. Only in exceptional circumstances should they be used without accurate measurement of central venous and arterial pressure and, ideally, pulmonary arterial and wedge pressure and the cardiac output should be monitored too. These measurements are particularly necessary (a) if the haemodynamic defect is uncertain or complex (e.g. haemorrhage in the presence of left heart failure); (b) if there is a marked discrepancy between the performance of the two sides of the heart (Leading Article, 1978d); (c) if myocardial function is known to be profoundly and acutely impaired and the balance between reduction in pre-load and after-load is critical. This last situation occurs most commonly following myocardial infarction and cardiopulmonary bypass and it is fortunate that such patients are often nursed in units where facilities exist for invasive monitoring.

Table II lists the concentrations and customary rates of administration of many of the drugs described here. In general it is preferable to use a central venous catheter for the infusion, not only to ensure reliability but also to avoid local damage caused by extravasation—dopamine and noradrenaline being particularly dangerous. The suggestions for the use of these drugs which are given below are no more than an outline of when to select the various preparations and more detailed guidance on the management of particular conditions is contained in a number of recent reviews (Leading Article, 1974; Kouchoukos and Karp, 1976; Kuhn, 1978a, b).

TABLE II. *Common strengths and doses of drugs used to support the circulation. For all but dopamine the amount required in 500 ml is quoted, but for reasons of economy smaller amounts in a reduced volume of diluent may be preferable. *Initial dose: increase gradually if necessary; †note strong concentration to allow for wide dose range*

	Dose range (μg kg^{-1} min^{-1})	Average adult dose (μg min^{-1})	Common strength	Average dose (ml min^{-1})
Adrenaline	0.01–0.1	2.0	5 mg/500 ml	0.2
Noradrenaline	0.05–0.25	4.0	4 mg/500 ml	0.5
Isoprenaline	0.01–0.05	2.0	5 mg/500 ml	0.2
Salbutamol	0.1–0.5	10.0	20 mg/500 ml	0.25
Dopamine	0.5–>30	200*	200 mg/100 ml†	0.1
Dobutamine	0.5–10	200	500 mg/500 ml	0.2
Sod. nitroprusside	0.2–>1	20*	50 mg/500 ml	0.2
Glyc. trinitrate	0.5–1	50	Inconstant	—

If both cardiac output and arterial pressure are extremely low, the immediate choice should be an inotropic agent—adrenaline, isoprenaline or dobutamine. If coronary perfusion is thought to be critical and the diastolic arterial pressure remains low, noradrenaline may be helpful in the short term although on a long-term basis it is more logical to consider mechanical circulatory support such as aortic counter-pulsation (Kuhn, 1978).

If the cardiac output is small and the arterial pressure is normal or low with marked peripheral vasoconstriction and oliguria, a less powerful inotrope with vasodilator properties can be chosen. Dopamine in low doses has the advantage of selectively increasing renal and mesenteric blood flow, which is theoretically of value in septic shock (Lefer and Glenn, 1972), but clinical results have been disappointing (Winslow et al., 1973). Salbutamol, which dilates both essential and inessential vascular beds, has been used successfully (Yacoub and Boyland, 1973; Sharma and Goodwin, 1978) and is particularly valuable when severe vasoconstriction persists in a previously normal subject exposed to prolonged hypotension (e.g. from haemorrhage) or very severe hypoxaemia. If dopamine is selected, it should be remembered that the effects are dose-dependent and that individual susceptibility varies (Holzer et al., 1973). A low dose should always be used at the outset (Leading Article, 1977).

If the cardiac output is small, the arterial pressure normal or high, and the venous pressures high with evidence of systemic or pulmonary venous engorgement, it is logical to select a pure vasodilator such as sodium nitroprusside, particularly if it is thought necessary to avoid increasing myocardial oxygen requirements (Shah, 1977). If the cardiac output and arterial pressure are both relatively normal but venous engorgement is prominent, glyceryl trinitrate may be of greater value (Chatterjee and Parmley, 1977a).

If vasodilator drugs are selected, it is important to appreciate that they can also dilate the pulmonary vascular bed, so worsening arterial hypoxaemia if there is already a notable intra-pulmonary shunt (Colley and Cheney, 1977). In occasional patients the state of the pulmonary vasculature is critical and a pulmonary vasodilator (e.g. isoprenaline, salbutamol or sodium nitroprusside) is preferable to drugs which increase the pulmonary vascular resistance, such as dopamine or adrenaline (Holloway, Polumbo and Harrison, 1975; Mentzer, Alegre and Nolan, 1976). Care must also be taken to avoid excessive reduction in right ventricular preload unless the pulmonary vascular resistance is very markedly reduced at the same time.

Whichever drug is selected, the importance of careful monitoring cannot be over-emphasized and, for the reasons outlined already, particular care is necessary for patients known to suffer from ischaemic heart disease who are particularly vulnerable to unnecessary tachycardia.

When circulatory failure is severe and intransigent, it is tempting to consider drug combinations, occasionally because true synergism occurs (e.g. aminophylline and glucagon (Afonso et al., 1972)), more often in the hope of obtaining the benefits of both and the disadvantages of neither. The combination of a vasodilator with an inotropic agent devoid of chronotropic properties (e.g. sodium nitroprusside with either dobutamine or low-dose dopamine) is particularly attractive and short-term benefit has been reported (Goldberg, Hsieh and Resnekov, 1977; Mikulic, Cohn and Franciosa, 1977; Miller et al., 1977; Stephens, Dymond and Spurrell, 1978). However, it is all too easy to institute elaborate regimes with intriguing theoretical possibilities; to do so on an "ad hoc" basis and without adequate monitoring can only be described as folly.

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ANTI-ARRHYTHMIC DRUGS

I. W. CARSON, S. M. LYONS AND R. G. SHANKS

CARDIAC ARRHYTHMIAS

Disturbances of cardiac rhythm are frequently encountered both in the operating theatre and in the intensive care unit. The anaesthetist should be aware of the factors involved in the prevention of such arrhythmias, be able to diagnose the type of rhythm abnormality, discover its aetiology and initiate the appropriate primary treatment. Arrhythmias may affect myocardial performance to different extents, depending on the nature of rhythm, the presence of cardiac disease and the patient's general condition. Fortunately, the majority of rhythm disturbances can be explained in terms of autonomic nervous system imbalance and are of little clinical significance, seldom requiring the administration of antiarrhythmic drugs.

Cardiac arrhythmias may occur in the following conditions:

Pre-existing disease

Patients with coronary atheroma and subsequent ischaemic heart disease (Katz and Bigger, 1970; Perloth and Hultgren, 1975), hypertension (Prys-Roberts, Meloche and Foëx, 1971), rheumatic and congenital heart disease (Buckley and Jackson, 1961) are most likely to have some disturbance of rhythm during anaesthesia. Endocrine disorders such as thyrotoxicosis and phaeochromocytoma are well recognized as causing cardiovascular irregularities (Bird et al., 1969; Bingham, Elliott and Lyons, 1972; Stehling, 1974). The management of tetanus in the intensive care unit is often complicated by serious cardiac arrhythmias (Kerr et al., 1968).

Disturbances of normal physiology

In anaesthetic practice cardiac arrhythmias are most frequently associated with adverse changes of ventilation, notably hypoxia and hypercarbia (Price, 1960). The resulting respiratory acidosis stimulates the vasomotor areas in the brain stem, resulting in increasing sympathetic outflow and release of catecholamines. Another frequent source of excess sympathetic activity is surgical stimulation under light anaesthesia. It has long been known that arrhythmias may be initiated reflexly by sympathetic or parasympathetic activity. Disturbances in acid-base balance, both metabolic alkalosis (Lawson, Butler and Ray, 1973) and metabolic acidosis—the latter whether secondary to generalized hypoxia or regional hypoxia, such as coronary atheroma—are associated with abnormalities in cardiac rhythm. Extremes of temperature, both hypothermia (Lloyd and Mitchell, 1974) and malignant hyperpyrexia (Britt, 1972), are associated with an increased frequency of arrhythmias. Variation in the intracellular or extracellular concentrations of certain electrolytes may result in cardiac irregularities; hypokalaemia and hyperkalaemia in particular give rise to problems in patients on digitalis and in renal failure (Lowenstein, 1973; Vaughan and Lunn, 1973; Curry et al., 1976; Steiness and Olesen, 1976). The response to altered concentrations of sodium and calcium have been reviewed by Katz and Bigger (1970).

Pharmacological causes

Anaesthetic agents. The effect of anaesthetic agents on cardiac electromechanical activity has been reviewed recently (Pratila and Pratilas, 1978). Almost all anaesthetic agents depress the myocardium and the resulting hypotension may lead to rhythm changes. However, the intrinsic ability of anaesthetic agents to produce arrhythmias varies markedly. No volatile anaesthetic drugs currently available for clinical use produce cardiac arrhythmias when given in anaesthetic concentrations. However, certain agents such as cyclopropane (Lurie et al., 1958; Price et al., 1958) and trichloroethylene (Barnes and Ives, 1944) have been known to cause increased cardiac irritability

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when excessive concentrations are required. The presence of hypercarbia in spontaneously breathing patients anaesthetized with cyclopropane or halothane is a common cause of arrhythmias (Johnstone, 1950; Black et al., 1959). The surgical use of adrenaline infiltration to produce a dry operating field was soon recognized as a hazardous clinical procedure in association with certain volatile anaesthetics (Katz and Katz, 1966). Trichloroethylene, cyclopropane and halothane were particularly susceptible to this interaction. Other halogenated agents such as enflurane, methoxyflurane and fluroxene have a wider margin of safety in this situation (Katz and Bigger, 1970; Lippman and Reisner, 1974; Reisner and Lippman, 1975).

Muscle relaxants. Suxamethonium, especially on repeated administration, causes bradycardia and cardiac arrhythmias in adults and particularly in children (Leigh et al., 1957; Lupprian and Churchill-Davidson, 1960). The frequency of bradycardia and asystole may be reduced by pre-treatment with a non-depolarizing muscle relaxant (Mathias and Evans-Prosser, 1970) or an anticholinergic agent, although the use of atropine itself has been associated with tachydysrhythmias (Massumi et al., 1972). Major problems arise with the use of suxamethonium in patients with burns, trauma, uraemia and neuromuscular disorders. The rapid increase in serum potassium contributes to a large extent to the cardiovascular hazards (Tolmie, Joyce and Mitchell, 1967; Bali and Dundee, 1975; Ohmura, Wong and Shaw, 1976).

Digoxin can cause increased cardiac irritability, especially when toxic concentrations are attained. This effect is accentuated by hypokalaemia (Steiness and Olesen, 1976).

Surgical situations

The majority of surgically induced arrhythmias are reflex responses to sympathetic or parasympathetic stimulation. The oculocardiac reflex has been reported to occur with pressure on the eyeball or traction on the extraocular muscles (Berler, 1963; Alexander, 1975). The high frequency of cardiac irregularities during oral and dental surgery is well recognized (Miller et al., 1970; Alexander, 1971; Plowman, Thomas and Thurlow, 1974; Thomas, Kyriakou and Thurlow, 1978). Intracranial neurosurgical manipulation may cause changes in heart rate or rhythm, particularly and of greatest significance in posterior-fossa surgery, as a result of pressure or traction on the brain stem and cranial nerves (Michenfelder, Gronert and Rehder, 1969).

Traction on intra-abdominal and pelvic viscera has been reported as causing cardiac arrhythmia (Folkow et al., 1962). In surgery within the thorax (Wylie and Bowman, 1964) handling and stimulation of the pericardium, heart and aorta may produce transient irregularities of rhythm, often with a subsequent decrease in cardiac output. Instrumentation and manipulation of the larynx and trachea may result in cardiac arrhythmias which are of major interest to anaesthetists (King et al., 1951; Denlinger, Ellison and Ominsky, 1974).

Disturbances of cardiac rhythm may also be encountered in patients with invasive monitoring devices such as pulmonary artery balloon flotation catheters (Buchbinder and Ganz, 1976) and in patients with a pacemaker.

While most of these arrhythmias are controlled by removal of the exciting cause, those which do not respond will require pharmacological intervention. It is thus important before commencing anti-arrhythmic therapy to have an understanding of the electrophysiology of myocardial muscle and the conducting tissues, and the disturbances which are responsible for, or contributing to, cardiac arrhythmias (Lappas, Powell and Daggett, 1977).

CLASSIFICATION OF ANTI-ARRHYTHMIC DRUGS

Vaughan Williams has suggested that anti-arrhythmic drugs may possess one or more main classes of action (Vaughan Williams, 1970, 1974, 1975). The first consists of a direct membrane action reducing the entry of inward depolarizing current. This effect has been called "membrane-stabilizing", "quinidine-like" and "non-specific" and can be detected as an increase in electrical threshold, slowing of conduction velocity or a reduction of the maximum frequency at which cardiac muscle will follow an electrical stimulus. High concentrations of drug are generally required to produce effects. The most sensitive test to show this effect is to demonstrate, by microelectrode recording, a reduction in the maximum rate of depolarization in the absence of any effect on resting potential or prolongation of the action potential. Drugs with these effects (Class I action) on cardiac muscle also produce local anaesthesia in nerve, although greater concentrations are required for this effect.

Lignocaine and mexiletine have been shown to shorten the duration of the action potential. The relevance of this effect to the Class I anti-arrhythmic action of these drugs is unknown. Disopyramide and quinidine increase action potential duration slightly.

Drugs with Class I anti-arrhythmic action include lignocaine, quinidine, procainamide, phenytoin, mexiletine and disopyramide. Some of these drugs have additional properties and uses. Lignocaine is used as a local anaesthetic; phenytoin has anticonvulsant properties and is used for the treatment of epilepsy. Quinidine and disopyramide have atropine-like effects.

Some beta-adrenoceptor blocking drugs have Class I effects in addition to their action in blocking beta adrenoceptors. Drugs with this action are propranolol, oxprenolol, alprenolol, pindolol, metoprolol and acebutolol (Shanks, 1976). Practolol, sotalol, timolol and atenolol are devoid of Class I activity (table I). The reasons for the presence or absence of Class I activity in different beta-blocking drugs are unknown (Shanks, 1976). There has been controversy over the contribution of this Class I action to the therapeutic effects of beta-blocking drugs. The current view would appear to be that it does not contribute to the beneficial effects of these drugs, including the treatment of cardiac arrhythmias, because no difference has been shown between the effects of different beta-blocking drugs. Likewise, Class I actions do not appear to contribute to the adverse effects of beta-blocking drugs. These views have been confirmed by studies which have shown that the concentration of a beta-blocking drug required for Class I actions (in an isolated tissue bath) is much greater than is required to produce beta-adrenoceptor blockade and a therapeutic effect in man (Shanks, 1976).

The second class of anti-arrhythmic action consists of antagonism of cardiac sympathetic drive by presynaptic prevention of transmitter release (bretylium and reserpine), by post-synaptic receptor blockade (beta-blocking drugs) or by a central action. The most widely investigated and clinically used group of drugs having this effect are the beta-adrenoceptor blocking drugs. Initial studies indicated that pronethalol and propranolol were effective in animals in abolishing or preventing arrhythmias produced by catecholamines (Sekiya and Vaughan Williams, 1963; Howe and Shanks, 1966). When it was shown that these drugs had also Class I activity, the exact mechanism of the anti-arrhythmic action was unclear. Propranolol exists in laevo- and dextro-isomers, the generally used form consisting of equal parts of both isomers. While the L-isomer has about 100 times the beta-blocking activity of the D-isomer, both have equal Class I activity (Howe and Shanks, 1966; Dohadwalla, Freedberg and Vaughan Williams, 1969). The L-isomer has a much greater effect than the D-isomer in abolishing catecholamine-induced arrhythmia (Barrett and Cullum, 1968). In addition, beta-blocking drugs such as sotalol and practolol, which are devoid of Class I activity, are effective in abolishing sympathetically-induced arrhythmia (Dunlop and Shanks, 1968). Thus beta-adrenoceptor-blocking drugs have a specific anti-arrhythmic effect in animals, resulting from blockade of beta-adrenoceptors.

The third class of anti-arrhythmic drugs comprises those which prolong the duration of the action potential. Such an effect occurs after the administration of the anti-anginal drug, amiodarone, which has little or no effect on automaticity (Singh and Vaughan Williams, 1970; Rosenbaum et al., 1976). A similar effect has been shown by the prolonged administration of beta-blocking drugs to rabbits (Raine and Vaughan Williams, 1978) and man (Raine and Pickering, 1977).

Class IV anti-arrhythmic effect results from interference with the slow inward sodium current (Vaughan Williams, 1974). Verapamil is an example of a drug in this category.

EFFECTS OF DRUGS ON EXPERIMENTAL ARRHYTHMIA

In recent years extensive studies have been carried out on the effects of drugs on cardiac arrhythmias in experimental animals. These studies have been used for the development of new anti-arrhythmic drugs, for investigation of the mode of action of such drugs and as a possible predictor of the effects of a drug in patients. Several different types of arrhythmias have been used and full descriptions of these can be found elsewhere (Allen et al., 1972; Allen et al., 1977).

Ouabain-induced ventricular tachycardia

Observations are made in dogs anaesthetized by pentobarbitone and artificially respired with room air. With the electrocardiogram and arterial pressure being recorded, the drugs are given i.v. Ventricular tachycardia is produced by the i.v. injection of ouabain, a rapidly-acting digitalis glycoside, starting with 40 μg kg^{-1}, 30 min later 20 μg kg^{-1} and then 10 μg kg^{-1} every 15 min until the tachycardia is produced. Observations have shown that this ventricular tachycardia will persist for at least 150 min. Ten minutes after the tachycardia is produced, the test drug is administered by continuous i.v. infusion until sinus rhythm returns or no response has occurred after infusion for 100 min. Drugs with Class I actions are effective in abolishing ouabain-induced arrhythmias (Dunlop and Shanks, 1968; Allen, Shanks and Zaidi, 1971; Allen et al., 1977). Thus lignocaine, mexiletine and propranolol are effective, but practolol is not. The relevance of this type of acute digitalis-induced ventricular tachycardia to the arrhythmias produced by digitalis toxicity in man is not known.

Halothane–adrenaline arrhythmias

Observations are made in dogs anaesthetized with pentobarbitone and artificially respired with room air and 1.0% halothane. Fifteen minutes later adrenaline 0.2 $\mu g\ kg^{-1}$ is injected i.v. The dose of adrenaline is progressively increased until a dose of adrenaline is obtained which produces a burst of self-terminating ventricular tachycardia or multifocal ventricular ectopic beats lasting about 20–30 s. After the test dose of adrenaline which produces an arrhythmia has been established, the test compound is injected i.v. Five minutes later the adrenaline challenge is repeated using the same dose. Increasing doses of the test compound are given to determine the minimum dose that prevents the adrenaline challenge from producing any ectopic beats. Beta-adrenergic-blocking drugs are most effective in preventing arrhythmias of this type (Allen and Shanks, 1974). Although drugs with Class I actions are effective, considerably larger doses (10–20 times) are required than for beta-adrenoceptor-blocking drugs (Allen, Shanks and Zaidi, 1971).

Arrhythmia after coronary artery ligation

Observations are made in dogs anaesthetized with methohexitone and respired with room air and halothane. The heart is exposed through an incision in the fourth or fifth left intercostal space and the left anterior descending coronary artery dissected free 2 cm below the tip of the left atrial appendage and ligated in two stages as described by Harris (1950). The chest is then closed in layers and the dog allowed to recover. Further observations are made 18–44 h after ligation of the coronary artery when the animal is conscious and the electrocardiogram recorded. At this time all dogs have developed a severe ventricular arrhythmia consisting of multifocal ventricular tachycardia interspersed with normal sinus beats. Drugs are administered by continuous i.v. infusion or by a series of increasing doses until the arrhythmia is abolished or adverse effects occur. Drugs with Class I actions, for example lignocaine, phenytoin, mexiletine and propranolol, are effective in abolishing this arrhythmia whereas drugs such as practolol, which has no Class I effect, are ineffective (Allen, Shanks and Zaidi, 1971; Allen et al., 1972; Allen and Shanks, 1974).

Threshold current for ventricular fibrillation

Allen and his colleagues have recently described methods for studying the effects of anti-arrhythmic drugs on the threshold current for ventricular fibrillation in anaesthetized dogs (Allen et al., 1977). Observations are made in the normal myocardium and in an area of ischaemic myocardium. Lignocaine and mexiletine, drugs with Class I actions, increase the threshold current for ventricular fibrillation in both situations. Measurement of the plasma concentrations of the drugs at the time when there was a doubling of the current required to produce ventricular fibrillation showed that the plasma concentrations are similar to those required in man for a therapeutic effect (Allen et al., 1977).

These studies in experimental arrhythmia show that the drugs with Class I actions are effective in abolishing or preventing the arrhythmias produced by ouabain and coronary artery ligation. These drugs are also effective in the same dose range in preventing the arrhythmia produced by adrenaline. Presumably this effect also results from their Class I actions. In contrast, much smaller doses of beta-adrenoceptor-blocking drugs, irrespective of the possession of Class I activity, are effective in preventing adrenaline-induced arrhythmias. It would appear that, in clinical practice, drugs such as lignocaine abolish cardiac arrhythmias through their Class I actions and beta-blocking drugs through their Class II effects. The actions of drugs with Class III and IV actions have not been investigated in a similar way in experimental arrhythmias, and the results correlated with their effects in patients.

ASSESSMENT OF THE EFFICACY OF ANTI-ARRHYTHMIC DRUGS IN MAN

In recent years increasing use has been made of drugs for the prevention and control of cardiac arrhythmia especially those occurring after acute myocardial infarction. During this time several new drugs including mexiletine, disopyramide and the beta-adrenoceptor-blocking drugs have become available for the treatment of cardiac arrhythmia.

Formerly the effects of a drug on cardiac arrhythmias were assessed by observation of the electrocardiogram before and for a few minutes after drug administration. Continuous recording of the electrocardiogram in patients with frequent and complex premature ventricular contractions (PVC) has shown that large variations in the total number of PVC can occur from one half-hour to the next (Winkle, 1978). In some patients the spontaneous variations in ventricular ectopic rate was such that, if a single dose of an anti-arrhythmic drug had been given at the end of the test period, it might have been concluded that the spontaneous effect had been caused by the drug. Similar variations occur on longer periods of observation. These results indicate that, in assessing the effect of a drug on cardiac arrhythmias, sufficient care must be used to ensure that changes in an arrhythmia are in fact drug-induced. The introduction of facilities for the continuous recording of the electrocardiogram over periods of 24 h and computer analysis has greatly facilitated the study of anti-arrhythmic drug effects (Murray, Campbell and Julian, 1978). In particular, computer analysis has enabled the processing of a greater amount of data and has been a marked improvement on continuous observer monitoring of the electrocardiographic records replayed and displayed at a fast speed. The introduction of continuous ambulatory monitoring systems has also greatly facilitated studies in patients both in hospital and while ambulatory.

For many years standardized dosage regimes were used for the administration of anti-arrhythmic drugs. With the introduction of methods and facilities for the measurement of plasma concentrations of these drugs, it was seen that the same dose produced wide variations in steady-state plasma concentrations between patients. Koch-Weser and Klein (1971) showed in patients receiving procainamide 3 g day^{-1} that the plasma concentrations ranged from less than 2 μg ml^{-1} to greater than 11 μg ml^{-1}. They also established that the therapeutic plasma concentration of procainamide was between 4 and 8 μg ml^{-1}. Thus some patients had a sub-therapeutic plasma concentration while others had a concentration which was associated with an increase in adverse effects. As a result of such studies, dosage regimes could be implemented to fit each patient more accurately and if an inadequate response or adverse effects were occurring, a determination of plasma concentration could be carried out and if necessary the dose altered.

A similar situation may occur with lignocaine where measurement of the plasma concentration after the i.v. administration of the conventional dose regime of a bolus of 100 mg followed by constant i.v. infusion at 2 mg min^{-1}, showed inadequate plasma concentrations during the first hour of therapy (Campbell et al., 1978a). As a result of such studies, new dosage regimes have been described for lignocaine (Aps et al., 1976).

Appreciation of the importance of measuring plasma drug concentrations has been utilized in the development of dosage regimes for new drugs. This is of particular importance for i.v. administration where a therapeutic plasma concentration should be provided at an early stage of treatment and maintained throughout treatment. Such principles were used in the development of mexiletine, as a method of measurement of the plasma concentration was available at an early stage of clinical investigation, and as a result the therapeutic plasma concentration and adequate dosage régimes were quickly defined (Shanks, 1978).

ANTI-ARRHYTHMIC DRUGS

Lignocaine

Lignocaine has been a most valuable drug for the treatment of ventricular arrhythmias, although it is only effective on parenteral administration. Lignocaine was initially introduced and used as a local anaesthetic agent until Southworth and colleagues (1950) successfully reversed ventricular tachycardia and ventricular fibrillation during cardiac catheterization by the administration of lignocaine.

Lignocaine has Class I anti-arrhythmic actions and is a potent local anaesthetic. It is effective against a wide range of ventricular arrhythmias, but is generally ineffective in suppressing atrial arrhythmias (Harrison, Sprouse and Morrow, 1963). The therapeutic plasma concentration of lignocaine is 2.0–5.0 μg ml^{-1} (Koch-Weser, 1972). Approximately 70% of the lignocaine entering the liver is metabolized on a single pass through the liver (Stenson, Constantino and Harrison, 1971). Thus lignocaine clearance is critically dependent on liver blood flow. Less than 3% of a dose of lignocaine appears in the urine. Lignocaine disposition has been described by a linear, two-compartment open model. In normal subjects the half-life of the distribution phase is 8 min and of the elimination phase 108 min (Boyes et al., 1971).

The pharmacokinetics of lignocaine may be altered by disease states. In patients with cardiac failure long-term infusions may produce 50% greater plasma concentrations. Thus in such patients the dose of lignocaine may require a reduction to reduce the occurrence of adverse effects. In patients with chronic liver disease, the clearance of lignocaine may be reduced, and the rate of administration may need to be reduced to prevent adverse effects (Harrison, Meffin and Winkle, 1977).

Lignocaine is generally given by i.v. injection, but has been given by i.m. injection in general practice to cover the period of transportation from home to hospital. Studies have shown that lignocaine 100 mg given i.v. and 300 mg by i.m. injection into the deltoid muscle in patients with acute myocardial infarction, maintained blood concentrations in the therapeutic range for at least 2 h (Barber et al., 1977).

In patients without cardiac failure, the widely used regime for the administration of lignocaine is an i.v. bolus injection of 100 mg followed by a constant i.v. infusion of 2 mg min^{-1}. A steady-state plasma concentration of between 2 and 4 $\mu g\ ml^{-1}$ is generally obtained within 2–3 h. Recurrence of arrhythmia is treated by the i.v. injection of 25–50 mg bolus. Recently it has been shown that with this regime the plasma concentration is small ($<2.0\ \mu g\ ml^{-1}$) about 45–60 min after this drug administration is commenced (Aps et al., 1976; Campbell et al., 1978a). These authors have recently suggested that this trough could be prevented by the administration of a larger dose of lignocaine during the first part of the infusion. Aps and his colleagues (1976) have recommended that the bolus injection is followed by an infusion rate of 4 mg min^{-1} for 30 min, 2 mg min^{-1} for 2 h and then 1 mg min^{-1} throughout the remainder of the infusion. Campbell and his colleagues (1978a) have recommended an initial bolus of 75 mg followed by an infusion of 10 mg min^{-1} for 20 min followed by 1.5 mg min^{-1}.

With therapeutic plasma concentrations (2–5 $\mu g\ ml^{-1}$) lignocaine exerts no cardiac depressant effect and does not alter heart rate or arterial pressure and has minimal effects on the cardiac conducting system (Harrison, Meffin and Winkle, 1977). Increased plasma concentrations ($>9.0\ \mu g\ ml^{-1}$) may produce adverse effects in the central nervous system including dizziness, tinnitus, respiratory arrest and grand mal seizures.

Procainamide

Procainamide possesses Class I anti-arrhythmic actions and is used to treat atrial and ventricular arrhythmias. It is quickly and completely absorbed from the gastrointestinal tract. Approximately 50% of an administered dose is recovered in the urine as unchanged procainamide (Koch-Weser, 1971). The liver metabolizes procainamide to N-acetylprocainamide (NAPA) which has anti-arrhythmic properties and is excreted by the kidneys (Giardina et al., 1976). The rate of acetylation of procainamide to NAPA shows a bimodal distribution with patients being classified as slow and fast acetylators (Reidenberg et al., 1975). The rate of acetylation parallels that of isoniazide, hydrallazine and dapsone (Gibson et al., 1975).

The plasma elimination half-life of procainamide is about 3.5 h (Winkle, Glantz and Harrison, 1975). Patients with impaired renal function and low cardiac output may eliminate procainamide more slowly and should receive a smaller dose. The oral administration of the same dose of procainamide may produce great differences in plasma concentrations (Koch-Weser and Klein, 1971). The exact reasons for this variation are not clear, but include individual differences in completeness of absorption, distribution space and elimination rate. These authors have suggested that in most patients a total daily dose of 50 mg/kg of body weight should produce therapeutic plasma concentrations. The usual effective anti-arrhythmic plasma concentration is 4–8 $\mu g\ ml^{-1}$ with toxic effects occurring commonly with concentrations greater than 16 $\mu g\ ml^{-1}$ (Koch-Weser and Klein, 1971).

Procainamide is generally administered orally for the control of cardiac arrhythmias and as it has a rapid rate of elimination should be administered 3-hourly to prevent large swings between peak and trough plasma concentrations. Although such a regime may be used in hospital, it is not practical elsewhere as patients may have difficulty wakening in the middle of the night to take a dose. A sustained release preparation of procainamide has now become available and initial studies indicate that with 8-hourly administration of 1.5 g, satisfactory plasma concentrations are maintained (Birkhead et al., 1976).

Minor side-effects produced by procainamide include nausea, vomiting, skin rashes, diarrhoea, mental depression and insomnia. Rapid i.v. injection may produce hypotension and a decrease in cardiac output. Long-term use (greater than 3 months) may produce a lupus-like syndrome with skin rash, fever, arthritis, arthralgia, pleuritic chest pain and pericarditis. Anti-nuclear antibodies develop in at least half of the patients receiving long-term procainamide therapy (Winkle, Glantz and Harrison, 1975). These features generally develop after oral administration of procainamide for at least 1 month and probably occur in up to 20% of patients receiving the drug. The syndrome generally disappears slowly after the drug is stopped. Procainamide is now not generally used for periods of treatment exceeding 1 month.

Diphenylhydantoin (phenytoin)

Phenytoin has anti-convulsant properties and is widely used as an effective drug in the treatment of epilepsy, but it is also effective in the control of supraventricular tachycardia and many ventricular arrhythmias, especially those associated with digitalis toxicity (Conn, 1965; Stone, Klein and Lown, 1971). Phenytoin has Class I anti-arrhythmic actions.

Phenytoin is largely metabolized in the liver, with 50–75% being excreted in the urine in a conjugated form; less than 5% appears in the urine as unchanged phenytoin. Phenytoin is excreted relatively slowly with a plasma elimination half-life of about 22 h, but because of non-linear kinetics the half-life is longer at high blood concentrations and shorter at small blood concentrations (Arnold and Gerber, 1970). There is a wide range of plasma concentrations for a given dose in patients and it is often desirable to measure the plasma concentration to ensure that it is within the therapeutic range, which is generally considered to be 10–18 μg ml^{-1} (Bigger, Schmidt and Kutt, 1968). The effect of disease states on the pharmacokinetics is apparently still controversial (Harrison, Meffin and Winkle, 1977).

Phenytoin can be administered i.v. in an emergency, but is generally given orally. The recommended dose for i.v. use is 50–100 mg every 5 min, or until the arrhythmia is controlled, toxicity occurs or 1000 mg has been given (Bigger, Schmidt and Kutt, 1968). The daily maintenance dose for oral administration is 300–400 mg, which can be given once a day.

The rapid i.v. administration of phenytoin may produce hypotension, ventricular fibrillation, asystole, respiratory arrest and death (Harrison, Meffin and Winkle, 1977). These adverse effects probably arise from peripheral vasodilatation and myocardial depression (Mixter, Moran and Austen, 1966). Adverse effects occurring with oral administration of phenytoin include nausea, vertigo, rashes, gingival hyperplasia, megaloblastic anaemia and peripheral neuropathy. The frequency and severity of some of these adverse reactions is related to the plasma concentration of phenytoin.

Beta-adrenoceptor-blocking drugs

Beta-adrenoceptor-blocking drugs first became available for the treatment of angina pectoris and cardiac arrhythmias in 1964 and were later shown to be of value in the treatment of hypertension. Propranolol was the first beta-adrenoceptor blocking drug to be widely used and is still the reference drug against which all others are still compared. Several other beta-blocking drugs have become available in recent years, although these are not necessarily available in all countries. Table I lists the beta-blocking drugs currently available in the British Isles. Some of these are also available in slow-release formulations and in combination with a diuretic.

TABLE I. *Properties of beta-adrenoceptor-blocking drugs*

Drug	Membrane activity	ISA	Cardio-selectivity
Sotalol	−	−	−
Timolol	−	±	−
Propranolol	+	−	−
Alprenolol	+	+	−
Oxprenolol	+	+	−
Pindolol	+	+	−
Practolol	−	+	+
Atenolol	−	−	+
Metoprolol	+	−	+
Acebutolol	+	+	±

Beta-blocking drugs differ from each other in several ways:

Potency. There are variations in the activity of these drugs in blocking beta-adrenoceptors in the heart. Such differences have been shown in animal studies and in man and also in their therapeutic use. These differences are not important in the clinical use of these drugs.

Membrane stabilizing activity. Propranolol and some other beta-blocking drugs are potent local anaesthetics and have an effect on cardiac cells characterized by a reduction in the maximum rate of depolarization. Similar effects are produced by drugs with Class I anti-arrhythmic actions. The occurrence of membrane stabilizing activity in beta-blocking drugs is shown in table I. Membrane stabilizing activity does not contribute to the therapeutic actions or the adverse effects produced by beta-blocking drugs.

Intrinsic sympathomimetic activity (partial agonist activity). In animals depleted of noradrenaline the administration of some beta-blocking drugs will increase heart rate (Shanks, 1976). This effect has been termed intrinsic sympathomimetic activity (ISA) or a partial agonist action. Some, but not all, beta-blocking drugs possess this effect (table I). There is no convincing evidence that this effect contributes to the actions of beta-blocking drugs in man.

Cardioselectivity. Practolol was shown to block selectively beta-adrenoceptors in the heart, while having much less effect on the beta-receptors in the bronchi (Dunlop and Shanks, 1968). Two other beta-blocking drugs, atenolol and metoprolol, have also been shown to be cardioselective (table I). The advantage of these drugs is that they are less likely to produce bronchospasm in patients with asthma. Practolol is no longer available as it produced severe adverse effects on long-term oral administration, which have been designated the oculomucocutaneous syndrome.

Beta-adrenoceptor blocking drugs have been shown to be of value in the treatment of atrial fibrillation by slowing the ventricular rate, supraventricular tachycardia, ventricular ectopic beats and ventricular tachycardia. As several beta-adrenoceptor blocking drugs are available it is not practical to discuss pharmacokinetic details, dosage regimes and adverse reactions in this article.

Many excellent review articles on the actions and uses of beta-adrenoceptor-blocking drugs have been published recently (McDevitt, Shanks and Prichard, 1976; Prichard, McDevitt and Shanks, 1976; Supplement, 1976; Avery, 1977; Braunwald, 1978). These should be consulted for more detailed information about this group of drugs.

Mexiletine

Mexiletine is a new anti-arrhythmic drug introduced in the British Isles in 1976. Animal studies show that it has Class I actions and is effective in abolishing experimental arrhythmias in animals and in increasing the threshold for ventricular fibrillation (Allen et al., 1977; Shanks, 1977, 1978). Mexiletine has no sympathetic blocking actions and does not prolong the duration of the action potential.

The pharmacokinetics of mexiletine in healthy volunteers and patients have been extensively studied (Prescott, Pottage and Clements, 1977; Campbell et al., 1978b, c). These studies have shown that mexiletine is well absorbed on oral administration, giving a high systemic availability. In normal volunteers, an oral dose of 200 mg produces peak plasma concentrations of 0.3–0.5 $\mu g\ ml^{-1}$ within 2–4 h. The absorption of mexiletine is delayed and is apparently less complete in patients with acute myocardial infarction; these changes may be further affected by the prior administration of narcotic analgesics (Prescott, Pottage and Clements, 1977).

After bolus i.v. injection plasma concentrations of mexiletine decrease rapidly as a result of extensive uptake and distribution in the tissues. This decline in the plasma concentration appeared to be the resultant of at least three exponential processes, representing fast and slow distribution phases with a much slower elimination phase. The disposition kinetics of mexiletine are consistent with a three-compartment model: the first "central" compartment probably consists of the blood volume and rapidly equilibrating highly perfused tissues such as myocardium, brain, liver, kidney and lung, while the second and third compartments represent "deep" or "peripheral" tissues such as skin, muscle and fat, which take up the drug more slowly. After distribution the plasma concentration of mexiletine decreases exponentially to give a mean plasma half-life in healthy subjects of 10–11 h with i.v. administration and 9–10 h with oral administration. The mean half-life determined in patients stopping chronic oral therapy was 12–13 h (Prescott, Pottage and Clements, 1977; Campbell et al., 1978b, c).

Mexiletine is eliminated from the body primarily by metabolism, which presumably occurs in the liver. In healthy volunteers a mean of 7.9% of an administered dose of mexiletine was recovered unchanged from the urine in 3 days (Prescott, Pottage and Clements, 1977).

The therapeutic plasma concentration of mexiletine is in the range of 1–2 $\mu g\ ml^{-1}$. Dose regimes for its administration have been described by Prescott and his colleagues (Prescott, Pottage and Clements, 1977). For i.v. use a bolus injection of 150–250 mg should be given over 2–5 min followed by a loading infusion of 250 mg in 30 min, then 250 mg in 2½ h and then 500 mg in 8 h. A maintenance infusion of 500–1000 mg is required each 24 h. This and similar regimes have been shown to maintain the plasma concentration in the therapeutic range during the period of administration. For oral administration the therapeutic plasma concentration can be maintained with 200–300 mg every 6–8 h. A loading dose of 400 mg may be given at the start of oral treatment and in patients with acute myocardial infarction an additional dose of 200 mg may be given at 2 h.

Mexiletine on oral and i.v. administration is effective in suppressing ventricular ectopic beats and ventricular tachycardia occurring after acute myocardial infarction and with digitalis toxicity, ischaemic heart disease and idiopathically (Campbell et al., 1973; Talbot et al., 1973; Talbot, Julian and Prescott, 1976; Campbell, Pantridge and Adgey,1978).

In a controlled trial the effects of mexiletine were compared against procainamide and placebo, in patients who had sustained a myocardial infarction and had received lignocaine for ventricular tachycardia or ventricular ectopic beats which were R–on–T, multiform or close-coupled (Campbell et al., 1975). Patients received mexiletine 250 mg 8-hourly, procainamide 500 mg 4-hourly or placebo for 12 days with 24-h e.c.g. monitoring on the 4th and 10th days. Seventy-seven per cent of patients receiving placebo showed serious ventricular rhythm disorders compared with 33% receiving anti-arrhythmic therapy. No major adverse effects occurred in the mexiletine-treated group. In another double-blind study, mexiletine or placebo were given to 165 patients on arrival in a coronary care unit with continuous recording of the electrocardiogram to document arrhythmia. Ventricular tachycardia and R–on–T ventricular ectopic beats were significantly reduced in the mexiletine-treated patients (Campbell et al., 1979).

The i.v. administration of mexiletine may produce small changes in heart rate, cardiac output and arterial pressure, but there was not a marked negative inotropic effect (Banim et al., 1977; Pozenel, 1977). In severely ill patients large i.v. doses of mexiletine may produce bradycardia and hypotension (Talbot et al., 1973). The side-effects which may occur with mexiletine are nausea, tremor, nystagmus, confusions and convulsions (Bell, 1978).

Disopyramide

Disopyramide is a new anti-arrhythmic drug which has been available in the British Isles for about 4 years. It has Class I actions on isolated heart preparations and also has vagolytic actions in animals and man (Mokler and Van Arman, 1962; Sekiya and Vaughan Williams, 1963; Davies, Marrott and Muir, 1979).

Disopyramide is well absorbed after oral administration with almost equal hepatic (metabolic) and renal clearances, although the metabolism is not yet completely understood (Hinderling and Garrett, 1976). After i.v. administration the terminal phase of the elimination phase had a half-life of 4.5 h (Hinderling and Garrett, 1976). The therapeutic plasma concentration is 3–8 μg ml^{-1}. The recommended dose for oral administration is 100 mg 6-hourly. Disopyramide has been shown to be more effective than a placebo in reducing the frequency of ventricular arrhythmias occurring in patients studied with ambulatory arrhythmia monitoring (Vismara, Mason and Amsterdam, 1974).

In a comparison of disopyramide with placebo in patients with acute myocardial infarction admitted to ordinary medical wards (Zainal et al., 1977), the mortality was much less in the disopyramide-treated group than in the placebo group. The comparability of the two groups in this trial has been questioned (*Lancet*, 1979).

The main side-effects produced by disopyramide result from its anti-cholinergic effects. These are dry mouth, dry eyes and urinary retention. The increase in heart rate which occurs after i.v. administration probably has a similar origin (Davies, Marrott and Muir, 1979). Further experience with this drug, especially on i.v. administration, is desirable.

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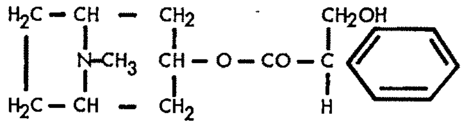
ANTICHOLINERGIC DRUGS

R. K. MIRAKHUR

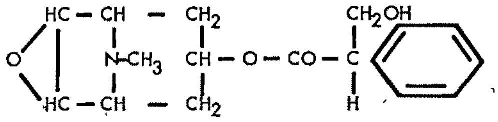
The use of anticholinergic drugs in anaesthetic practice is deep-rooted and widespread. Atropine, the classical representative, antagonizes all the muscarinic actions of acetylcholine. The drugs of this class may in fact be more appropriately termed "antimuscarinic" drugs, since most show a highly selective antagonism at muscarinic receptors (Eger, 1962; Innes and Nickerson, 1975). Though many drugs with similar properties have been in use from time to time, atropine and hyoscine are still the mainstay as revealed by a recent survey (Mirakhur et al., 1978a).

Chemistry

Atropine and hyoscine are esters of the complex organic bases tropine and scopine respectively, with tropic acid. The two drugs differ by the presence of an oxygen bridge in hyoscine (fig. 1). Both are tertiary compounds; however, their quaternary derivatives and indeed most other quaternary antimuscarinic drugs are in general more potent.



DL-HYOSCYAMINE (Atropine)



L-HYOSCINE (Scopolamine)

FIG. 1. Structural formulae of atropine and hyoscine.

Atropine is a mixture of equal parts of D- and L-hyoscyamine, although the D-form does not contribute to its anticholinergic activity. Hence atropine is only half as potent as its L-isomer, the pure preparations of which are known as Bellafoline. Commonly used preparations of hyoscine contain only its L-isomer, D-hyoscine having little or no activity. Drugs with anticholinergic properties have diverse chemical structures and their structure–activity relationship is complex (Stoll, 1948; Innes and Nickerson, 1975).

Mechanism of action

The mechanism of action of atropine-like drugs is by competitive antagonism to the actions of acetylcholine. The antagonism can be overcome by the administration of acetylcholine or anticholinesterase agents. Anticholinergic drugs do not undergo any chemical reaction with acetylcholine or affect its release or rate of hydrolysis (Ambache, 1955). The action takes place at nerve endings without blocking the transmission of impulses along the nerve fibres (Ambache, 1955) and most have a highly selective action at muscarinic receptors (Eger, 1962; Innes and Nickerson, 1975). Larger doses, however, may lead to effects on ganglionic and neuromuscular transmission (Tum-Suden, 1958).

The sensitivity of the various end-organs to the effects of atropine and hyoscine is different. While the lowest doses may be sufficient to inhibit salivation and sweating, large doses are necessary for action on cardiac vagus and smooth muscle of the gastrointestinal tract. According to Eger (1962) this may be the result of the release of the chemical mediator in some areas in closer proximity to the receptors. Herxheimer (1958) and Mirakhur (1978) have also shown that the effects on eye are late in onset and persist for longer periods.

Effects on cardiovascular system

The effects of atropine on the cardiovascular system have been exhaustively studied in man. Its actions on heart rate are particularly complex. Soon after its administration in 0.2–0.3-mg doses, a slowing of the heart rate is noticed (Morton and Thomas, 1958). Doses of 0.5 mg or less produce only a slowing of the heart rate (Thomas, 1965; Mirakhur, 1978),

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believed to be caused by the stimulation of the medullary cardio-inhibitory centre (Innes and Nickerson, 1975), although others consider this to be peripherally mediated (Lönnerholm and Widerlöv, 1975). According to a recent study (Das, Talmers and Weissler, 1975), the response of the S–A node itself is bimodal, slowing with smaller doses and accelerating with larger doses of atropine.

The main effect, however, is a progressive and dose-related increase in heart rate (Dauchot and Gravenstein, 1971). According to Chamberlain, Turner and Sneddon (1967) vagolytic activity at the S–A node can be produced by atropine 0.025–0.04 mg kg^{-1}. However, the degree of tachycardia following atropine administration is not consistently predictable even when given on a weight-adjusted basis (Boba, 1976). Boba also demonstrated a negative correlation between the initial heart rate and the increase following atropine administration. Under anaesthesia, however, even the smaller doses lead to tachycardia (Eger, 1962).

All the cardiac effects of acetylcholine and vagal stimulation such as prolongation of the P–R interval, decreased conduction and reduced cardiac output are reversed by atropine. Reflex vagal cardiac slowing as a result of inhalation of irritant vapours, stimulation of the carotid sinus, pressure on the eyeballs, pulling of extraocular muscles or peritoneal stimulation can be abolished by atropine (Johnstone, 1956; Leigh et al., 1957; Rocco and Vandam, 1957). Bradycardia following repeated administration of suxamethonium is also prevented by atropine. Atropine may accelerate the idioventricular rhythm in some patients with complete heart block (Gilchrist, 1933).

Arrhythmias such as A–V dissociation, A–V block, nodal rhythm and ventricular extrasystole have been reported following atropine administration (Averill and Lamb, 1959; Gravenstein, Ariet and Thornby, 1969). The arrhythmias can be dangerous since those associated with hypotension have been found to reduce the coronary artery blood flow (Corday et al., 1959). In general, arrhythmias can be more frequent under anaesthesia (Jones, Deutsch and Turndorf, 1961; Farman, 1967), but the frequency is smaller under thiopentone, nitrous oxide and oxygen anaesthesia (Eger, 1962). The frequency following atropine 0.4 mg i.v. is 17% under halothane anaesthesia, but as great as 54% during anaesthesia with cyclopropane.

Atropine is often used either before or with neostigmine at the time of reversal of the non-depolarizing neuromuscular block. Provided the oxygenation is adequate, administration of atropine by either method is safe. However, there is less tachycardia with the administration of the mixture (Ovassapian, 1969).

The effects of hyoscine on the heart rate are weak (Orkin, Bergman and Nathanson, 1956) although List and Gravenstein (1965) observed a short-lasting increase in heart rate followed by a secondary bradycardia. Heart rates under anaesthesia are greater following premedication with atropine as compared to hyoscine (Eger, Kraft and Keasling, 1961).

The effect of atropine and other anticholinergic drugs on arterial pressure in man is small. Moderate doses may, however, lead to a slight increase in arterial systolic pressure as a result of an increase in heart rate.

Vasodilatation of cutaneous vessels seen following atropine is thought to be unrelated to its antimuscarinic properties (Westfall, 1976).

The nervous system

The effects of atropine and hyoscine on the central nervous system (c.n.s.) are more unpredictable and variable (Shader and Greenblatt, 1972). Atropine in the usual doses produces no effect or a mild stimulation and doses of atropine in the range of 2–3 mg rarely cause toxicity (Cullumbine, McKee and Creasy, 1955; Longo, 1966). Moderate doses may depress certain motor mechanisms controlling muscle tone. Significant c.n.s. effects are believed to result after 5–10 mg (Shader and Greenblatt, 1972), when a bizarre picture of both c.n.s. excitation and depression with fluctuations develops to produce what is commonly called a "central anticholinergic syndrome".

The central potency of hyoscine is eight to nine times that of atropine (Westfall, 1976) and with the usual therapeutic doses, produces drowsiness, euphoria and sleep. The frequency of amnesia produced by diazepam is increased by hyoscine (Frumin, Herekar and Jarvik, 1976). Greater doses may lead to excitement, restlessness, confusion or other signs of central stimulation especially in the elderly. Very large doses can cause hallucinations and finally coma and death from respiratory paralysis. Physostigmine is highly effective in reversing the central effects including delirium. In spite of these possible drawbacks the sedative action of hyoscine is considered an additional advantage in premedication (Eger, Kraft and Keasling, 1961; Clarke, Dundee and Moore, 1964).

Respiratory system

Respiratory stimulant properties have been attributed to these drugs (Wangeman and Hawk, 1942) although others do not agree with such views (Steinberg, Bellville and Seed, 1957).

Both drugs relax the smooth muscles of bronchi and bronchioles, thus decreasing the airway resistance, although atropine is the more potent of the two. The increase in deadspace as a result of bronchiolar dilatation may have been the reason for oxygen desaturation observed by Tomlin, Conway and Payne (1964) following atropine premedication, although this was subsequently discounted (Nunn and Bergman, 1964).

The secretion of the bronchial glands is inhibited by atropine and even more by hyoscine and there is a decreased frequency of cough and laryngospasm at the induction of anaesthesia after these drugs are given (Clarke, Dundee and Moore, 1964). It seems likely that the drying effect of the anticholinergic agents is responsible for the inhibition of respiratory complications rather than any effect on the laryngeal muscles (Rosen, 1960).

Gastrointestinal tract

The smooth muscle tone in the gastrointestinal tract is reduced by atropine and hyoscine. Atropine decreases the amplitude and frequency of peristalsis of all segments (Alder, Atkinson and Ivy, 1942; Andrew, 1954). It also reduces the gastric acidity and total gastric secretion, although larger doses are necessary. The effects on gastric secretion are delayed and are always preceded by diminished salivation and other effects (Bachrach, 1958). Any antispasmodic effect on gall bladder and bile ducts is very weak.

Atropine and hyoscine possess antiemetic action (Isaacs, 1956; Dundee, Moore and Clarke, 1964; Clarke, Dundee and Love, 1965), although hyoscine is decidedly the more potent.

Atropine has now been shown conclusively to reduce the opening pressure of the lower oesophageal sphincter (Lind, Crispin and McIver, 1968; Skinner and Camp, 1968) thus increasing the chances of regurgitation.

Secretions

Reduction of salivary secretions is believed to be one of ths earliest effects of antimuscarinic drugs and can result even with their lowest doses (Herxheimer, 1958; Innes and Nickerson, 1975). The mouth becomes dry and swallowing and talking may be rendered difficult. There are, however, great individual variations (Mushin, Galloon and Lewis-Faning, 1953; Mirakhur, Dundee and Jones, 1978). Hyoscine (Scopolamine) is slightly more potent in this regard as judged both by measuring the salivary secretion and by administration to patients as a premedicant (West and Papper, 1950; Wyant and Dobkin, 1957). Atropine has been found satisfactory, although some observers reported variable effects (Wyant and Dobkin, 1957; Dobkin, Wyant and Aasheim, 1958).

Ocular effects

The mydriatic action of belladonna alkaloids is amongst their oldest known actions. Pupils enlarge in size, there is photophobia and the near point of vision recedes following both local and systemic administration. Hyoscine is again more potent than atropine. The ocular effects set in later and last longer, although larger doses may shorten the time of onset of ocular effects (Herxheimer, 1958). This is a result of the aqueous humour acting as a reservoir (Herxheimer, 1958) although Salazer and Patil (1976) think the longer action of atropine results from the slow release of bound drug from the pigment of the iris. A recent study has revealed the eyes of black people to be more resistant to the action of atropine than those of Caucasians (Garde et al., 1978).

The intraocular pressure is not increased in normal eyes, but can increase in glaucomatous eyes (Stoll, 1948), although Schwartz and his colleagues (1974) have shown that in doses used in premedication neither atropine nor hyoscine increases the intraocular pressure even in glaucomatous patients.

Effects on other systems

The normal tone of the genitourinary tract is reduced and a tendency towards urinary retention may develop (Cullumbine, McKee and Creasy, 1955).

An increase in body temperature occurs after administration of large doses especially in small children and infants, although Magbagbeola (1973) found no dangerous increase in normothermic children following atropine 0.2–0.6 mg, even in the tropics. Suppression of sweating in increased environmental temperatures is considered a contributing factor (Cullumbine and Miles, 1956), but large doses may be acting also via a central effect on the temperature regulating mechanism (Stoll, 1948). Hyperpyrexia is, however, one of the features of atropine poisoning (Mackenzie and Pigott, 1971; Gillick, 1974).

The use of atropine premedication for Caesarean section has recently been reported to produce a loss of beat-to-beat variation in the fetal heart (Taylor, 1977).

Pharmacokinetics

Being tertiary amines, the belladonna alkaloids are absorbed well from the gastrointestinal tract and mucosal surfaces (Westfall, 1976; Innes and Nickerson, 1975), although not from the stomach. The duodenum and jejunum are the main sites of absorption (Beerman, Hellstrom and Rosén, 1971). The absorption of atropine following oral administration is much better than that of hyoscine (fig. 2), atropine being about half as potent orally as by the i.m. route (Murrin, 1973; Mirakhur, 1978), but the oral dose of hyoscine needs to be five to six times the i.m. dose (Mirakhur, 1978). Distribution of atropine occurs throughout the body and across the blood–brain barrier and placenta (Kivalo and Saarikoski, 1977; Proakis and Harris, 1978).

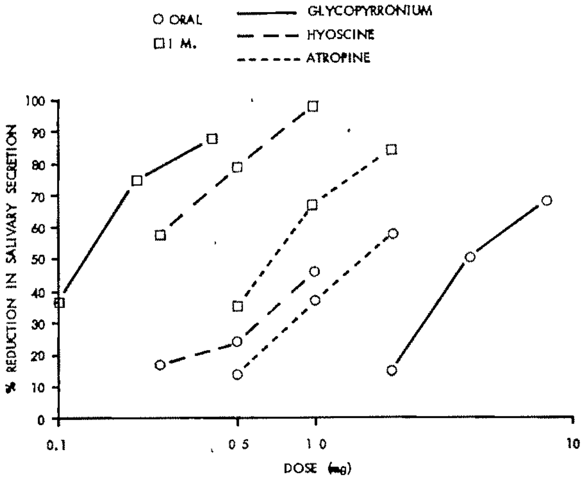


FIG. 2. Effects of oral and i.m. administration of atropine, hyoscine and glycopyrronium on salivary secretion (doses on log scale).

Enzymatic hydrolysis and conjugation in the liver are thought to comprise the main metabolic pathway of the belladonna alkaloids (Greene, 1968). Both atropine and hyoscine have been reported to be extensively metabolized (Brown and Geha, 1975). The latter authors observed biphasic plasma concentrations and two distinct half-lives of atropine, a rapid half-life of 1.5 h and a secondary phase 12–38 h later. The kidney is apparently the main channel of excretion (Kalser, 1971; Brown and Geha, 1975).

Overdose

The main features are dry mucosae, blurred vision, photophobia, hot, dry and flushed skin, high temperature and signs of the central anticholinergic syndrome such as delirium, excitement, hallucinations, ataxic gait, coma, fever and occasionally death. Treatment, apart from gastric lavage, is mainly symptomatic and administration of physostigmine (Mackenzie and Pigott, 1971; Gillick, 1974) or galanthamine (Cozanitis, 1977).

A case of suspected anaphylaxis has also been reported following atropine administration (Turner, Keep and Bartholomaeus, 1972).

OTHER ANTICHOLINERGIC DRUGS

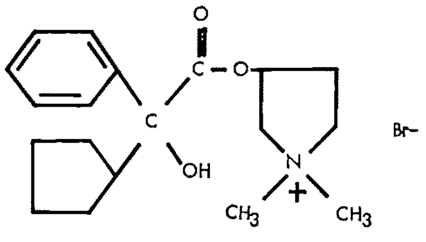
Although atropine and hyoscine are the mainstay of anticholinergic therapy, other agents have been studied from time to time, mainly from the point of view of their gastrointestinal effects.

Atropine and hyoscine are used extensively, but they suffer from disadvantages such as short duration of action, undesirable central effects, unreliable antisialogogue action of atropine and weak cardiac action of hyoscine. Ing, Dawes and Wajda (1945) assessed large numbers of drugs possessing anticholinergic properties particularly for effect on the gastrointestinal tract and the eye. Most of these never reached the clinician. The majority of the drugs evaluated have been quaternary ammonium compounds. Of the tertiary compounds, L-hyoscyamine (Bellafoline) was reported by Galloon (1956) and Wyant and Dobkin (1957) to be superior to atropine as a drying agent. It is twice as potent as atropine since it contains the L-isomer only, whereas atropine consists of equal portions of L- and D-isomers, the D-isomer having no activity. However, side-effects such as dizziness, excessive tachycardia and arrhythmia are common.

A vast number of quaternary compounds, including the quaternary salts of atropine and hyoscine, have been assessed. Scopolamine butylbromide was found to be an unreliable antisialogogue giving rise to excessive increase in heart rate (Möller and Rosén, 1968). In the studies by Herxheimer (1958) most of the quaternary compounds gave rise to greater degrees of tachycardia than atropine.

Methantheline (Banthine), propantheline (Probanthine) and oxyphenonium (Antrenyl) have been the most widely studied quaternary drugs. All are more potent and longer lasting than atropine, but possess proportionally greater ganglion-blocking and neuromuscular-blocking properties, a relationship shared by most other quaternary drugs. On the credit side, they are relatively longer-acting and do not have central and ocular effects. All are poorly absorbed from the gastrointestinal tract. The first two drugs were evaluated clinically by Stephen and colleagues (1956). No advantage over atropine could be demonstrated as premedicants, and both again produced greater degrees of tachycardia.

In a study of many drugs with antisialogogue action, Dobkin, Wyant and Aasheim (1958) and Wyant and Dobkin (1958) found that, when side-effects were taken into consideration, atropine and hyoscine were preferable to others.



GLYCOPYRRONIUM BROMIDE

(1-methyl-3-pyrrolidyl-phenyl-cyclopentane glycolate bromide)

FIG. 3. Structural formula of glycopyrronium.

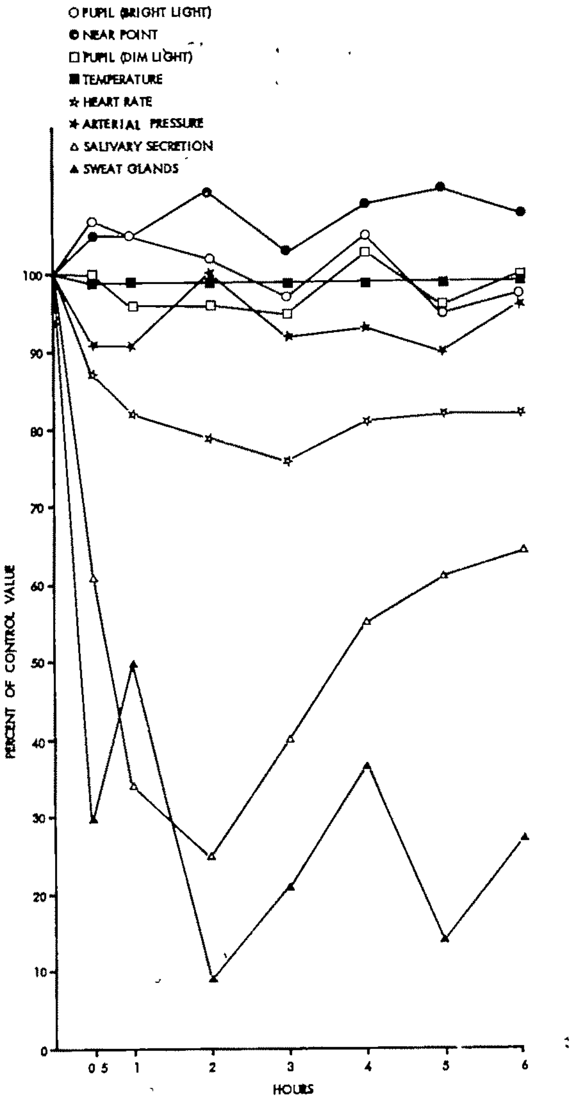


FIG. 4. Effects of glycopyrronium on various aspects of cholinergic function. Salivary secretion and sweat gland activity appear to be selectively affected.

More recently another quaternary ammonium compound, glycopyrronium bromide (glycopyrrolate USNF; fig. 3), has been evaluated for use in anaesthesia, although it had been used in the treatment of peptic ulcer for a number of years. The drug has been shown to possess potent antisialogogue action of long duration (Wyant and Kao, 1974; Mirakhur, Dundee and Jones, 1978). While Wyant and Kao found it to be twice as potent as atropine, more accurate assessment showed it to be about four or five times as potent as atropine in its antisialogogue action (Mirakhur, 1978; Mirakhur, Dundee and Jones, 1978). Its penetration across the blood–brain and placental barriers is poor (Proakis and Harris, 1978) and the drug is devoid of undesirable central actions possessed by the tertiary compounds. In the clinically useful doses selectivity of action on salivation and sweating is clearly demonstrated, leaving most other parameters unaffected (fig. 4). As a premedicant for minor surgery it showed no advantage over atropine (Mirakhur, Dundee and Connolly, 1979) although the drug was less arrhythmogenic than atropine in patients needing intubation (Mirakhur et al., 1978b). The most consistent superiority over atropine in terms of cardiovascular stability has been reported when it is used in combination with neostigmine for the reversal of competitive neuromuscular block (Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977). This advantage should perhaps be exploited to the full. The drug is currently undergoing extensive trials at various centres in the U.K. and in course of time will find a place in the anaesthetists' armamentarium. No serious side-effects have been reported and the drug could be used with advantage in premedicating elderly patients,

patients with concurrent cardiac disease and in association with neostigmine. Absorption of the drug following oral administration is, however, poor (fig. 2).

PRESENT POSITION

The main reasons given by anaesthetists for the use of anticholinergic drugs in premedication are the drying up of secretions and protection against vagal reflexes. These drugs have also been shown to have antiemetic action, to increase the tone of cardiac sphincter and to prevent laryngeal spasm (Dripps, 1944; Clark and Riddoch, 1962; Clarke, Dundee and Love, 1965). Modern anaesthetic agents and techniques, with the exception of ether, do not cause any great problem with secretions. Specific antiemetic agents are available for the prevention and treatment of sickness after operation. Rosen (1960) found atropine to be of no value in the treatment of laryngeal spasm. Atropine and other anticholinergic drugs have now been shown to decrease the opening pressure of the lower oesophageal sphincter (Lind, Crispin and McIver, 1968; Skinner and Camp, 1968; Brock-Utne et al., 1978). Atropine in addition produces arrhythmia of various types (Averill and Lamb, 1959; Jones, Deutsch and Turndorf, 1961; Eikard and Andersen, 1977).

The use of atropine in premedication was criticized by Holt (1962) and Inglis and Barrow (1965) many years back. Eger (1962) and Clarke, Dundee and Moore (1964) suggested avoiding anticholinergic premedication for minor surgical procedures—impressions confirmed recently (Mirakhur, Dundee and Connolly, 1979). Studies by Kessell (1974) and by Leighton and Sanders (1976) showed no adverse effects by omitting the routine use of anticholinergic premedicants. Arrhythmia during intubation was observed more often in patients who had received atropine in premedication (Mirakhur et al., 1978b). Increasing the pH of gastric contents by administration of comparatively larger doses of glycopyrronium has been shown by some workers (Baraka et al., 1977) but no such advantage over atropine was observed by others (Stoelting, 1978; Mirakhur, Reid and Elliott, 1979). The routine or rather mandatory use of atropine in obstetric anaesthesia should be re-investigated in view of the consistent reports of decreasing of oesophageal opening pressure with this drug. This is obviously conducive to the occurrence of regurgitation. In addition, the loss of beat-to-beat variation of the fetal heart takes away an important sign of early fetal hypoxia.

In spite of these findings, more than 60% of anaesthetists still use anticholinergic drugs routinely in premedication (Mirakhur et al., 1978a), but the trend is towards more rational use of these drugs and many anaesthetists are using them less often or giving them i.v. on induction. Good oral absorption of atropine also does not seem to be well known, although Joseph and Vale (1960) showed its clinical usefulness.

It is suggested that such drugs be used with more discrimination. There is little need to use them in minor surgical procedures and the need to use drugs such as atropine, even in patients needing tracheal intubation, should be reassessed in the light of recent work. There will be specific indications such as repeat administration of suxamethonium, bradycardia during operation, administration of an ether anaesthetic and, of course, with neostigmine at the time of reversal of non-depolarizing neuromuscular block. Minimal cardiovascular effects of the quaternary drug glycopyrronium may be an advantage. The patients' comfort commensurate with their safety should be the consideration. Infants and children may be treated separately. The presence of secretions in small airways may lead to an increase in airway resistance or even obstruction. The primary use of atropine in infants, however, is to counteract cholinergic challenges to the heart (Cook, 1976) and these patients are more likely to suffer bradycardia following administration of suxamethonium (Leigh et al., 1957). The drugs could be used i.v. if necessary.

The use of atropine-like drugs with neostigmine to counter its muscarinic actions has not been a matter of debate except perhaps for the timing of administration of the two drugs. According to the evidence available at the moment it appears that the administration of the mixture is associated with less serious cardiovascular effects than the previous practice of giving the atropine before the neostigmine. Glycopyrronium has a definite advantage over atropine in this respect.

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AIRWAY PHARMACOLOGY

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Airway pharmacology is predominantly concerned with the reversible aspects of airway narrowing. The progress made in the past few years in unravelling the intracellular biochemical events underlying smooth muscle contraction and mediator release from mast cells has been matched by improved techniques for studying airway function in intact man. This has increased our understanding of the way in which both physiological and pharmacological factors modify airway calibre, the two being closely interrelated since much of our knowledge of normal physiological control has been obtained by studying the effects of pharmacological agents such as propranolol or atropine. Since drugs exert their effect by modifying the physiological factors controlling airways size it seemed appropriate to start this article by discussing how these factors interact in normal subjects and how they appear to differ in patients with airways obstruction for whom the drugs are usually prescribed.

CONTROL OF AIRWAY CALIBRE

The drugs under review exert their main effect on the smooth muscle cell directly or via the autonomic nervous system, or they have an indirect effect through mast cells, mediators or mucociliary clearance. It must be remembered that other factors such as age or lung recoil pressure influence airway calibre, but since they are not normally amenable to change with pharmacological agents they are not discussed below.

Autonomic innervation

Normal subjects. In man airway smooth muscle has a rich parasympathetic innervation through the vagus. When stimulated this causes bronchoconstriction and resting vagal tone probably accounts for the slight bronchoconstriction normally present at rest. Anticholinergic drugs such as atropine cause bronchodilatation in normal subjects with a decrease in airway resistance (Butler et al., 1960) and an increase in anatomical deadspace (Severinghaus and Stupfel, 1955).

The sympathetic nerve supply to the lungs appears to be distributed to bronchial and pulmonary blood vessels rather than to bronchial smooth muscle (Widdicombe and Sterling, 1970). This is surprising, since bronchial smooth muscle is well supplied with beta-adrenergic receptors. It is possible that the bronchial smooth muscle effects of sympathetic stimulation are secondary to vascular constriction or overflow of mediators from vascular smooth muscle; alternatively the receptors may respond only to circulating catecholamines. In normal subjects there appears to be little if any resting sympathetic activity. Some early workers found changes in airway resistance after propranolol (MacDonald, Ingram and McNeill, 1967) but more recent studies have found no change in the majority of subjects (Richardson and Sterling, 1969; Tattersfield, Leaver and Pride, 1973; Gribbin, Baldwin and Tattersfield, 1979).

The sympathetic neurotransmitter, noradrenaline, is a catecholamine with strong alpha- and weak beta-agonist activity. Nevertheless, it causes bronchodilatation (a beta effect), emphasizing the overwhelming importance of beta-receptors in bronchial smooth muscle. It is still not clear whether alpha-receptors are present in the airways; recent studies in normal subjects have demonstrated little (Anthracite, Vachon and Knapp, 1971) or no evidence for their existence (Snashall, Boother and Sterling, 1978).

Asthma. Patients with asthma, like normal subjects, have evidence of resting vagal activity causing some bronchoconstriction at rest. Whether vagal activity is actually increased in asthma is controversial; there is no direct evidence for this and the rather poor response of these patients to atropine argues against it. Unlike normal subjects, asthmatic patients often bronchoconstrict with beta-adrenergic antagonists (McNeill, 1964; Benson et al., 1977). This provides evidence of resting sympathetic stimulation to bronchial beta-receptors whether as a result of increased activity of sympathetic nerves or of increased concentrations of circulating catecholamines. The sympathetic drive to the airways in asthma is

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analogous to the sympathetic drive to the heart in patients with heart failure.

Because several studies with alpha-receptor blocking drugs have demonstrated bronchodilatation, it has been suggested that alpha-receptors are of some functional importance in asthma (Bianco et al., 1974; Beil and de Kock, 1978). The results need interpreting with caution, however, because all alpha-blocking drugs have other relevant pharmacological effects such as beta-agonist activity, noradrenaline release and antihistaminic effects (Snashall, Boother and Sterling, 1978). In addition, they produce systemic hypotension which could cause secondary reflex autonomic effects on airway calibre. Nevertheless, patients with asthma have been shown to differ from normal subjects in having a bronchoconstrictor response to the alpha-agonist drug methoxamine following treatment with atropine and beta-blocking drugs (Snashall, Boother and Sterling, 1978). This may be as a result of stimulation of bronchial smooth muscle directly or of release of mediators following mast cell alpha-receptor stimulation (Kaliner, Orange and Austen, 1972). However, in view of the bronchodilating effects of noradrenaline it seems unlikely that increased alpha-receptor activity is of great importance in asthma.

Bronchial smooth muscle

Bronchial smooth muscle, wrapped in a spiralling network around bronchi and bronchioles, has several different surface receptors, although most is known about the adrenergic beta-2 and the acetylcholine receptor. The beta-2 receptor (fig. 1) is closely linked to the enzyme adenylate cyclase which, when stimulated, increases the formation of cyclic 3′5′-AMP (Sutherland and Robison, 1966). Increased concentrations of intracellular cyclic AMP are associated with bronchodilatation, although the exact way in which this is achieved is unknown. Cyclic AMP appears to activate specific phosphorylating enzymes, protein kinases, which probably interact with calcium to reduce actin–myosin coupling (Sands, Meyer and Rickenberg, 1973; Sobel and Mayer, 1973).

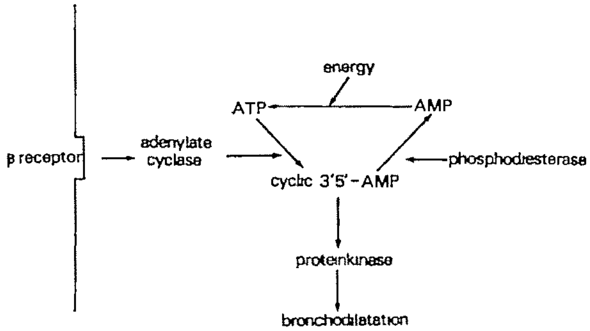

FIG. 1. Tentative model of relationship between the β-receptor, cyclic 3′5′-AMP and bronchodilatation.

Stimulation of acetylcholine receptors increases cyclic GMP in isolated tracheal preparations (Murad, 1974). The balance of cyclic AMP and cyclic GMP may be important in regulating smooth muscle contraction although there is some evidence that cyclic GMP plays a less direct role, since concentrations appear to increase after actin–myosin coupling has taken place (Goldberg, Haddox et al., 1975). Both cyclic AMP and cyclic GMP are broken down by phosphodiesterases and the concentration of both cyclic nucleotides will be increased by phosphodiesterase inhibitors such as theophylline. The bronchodilating properties of theophylline have been attributed to decreased breakdown of cyclic 3′5′-AMP, although some recent work has suggested that relatively little phosphodiesterase inhibition will occur at the therapeutic theophylline concentrations achieved in man (Polson et al., 1978). Their mode of action may be more complex.

Less is known about other pharmacological receptors such as those for histamines, serotonin, slow reacting substance of anaphylaxis and prostaglandin, although prostaglandin E also appears to activate adenylate cyclase and increases cyclic AMP concentrations. In normal subjects and most asthmatic subjects it causes bronchodilatation (Mathé and Hedquist, 1975; Smith, Cuthbert and Dunlop, 1975).

Mast cells and mediators

Mast cells lying in close proximity to airway smooth muscle contain surface receptors with a high affinity for IgE (Ishizaka and Ishizaka, 1977). Subsequent exposure of the mast cell to the appropriate antigen or anti-IgE causes bridging across the IgE molecules and initiation of a series of intracellular biochemical changes leading to mediator release. Evidence from peripheral leucocytes suggests that these events are controlled by cyclic 3′5′-AMP and probably cyclic 3′5′-GMP and can therefore be modified by hormones or drugs. Beta-adrenergic agonists, methylxanthines and prostaglandin E increase cyclic AMP and inhibit mediator release; prostaglandin $F_{2}\alpha$ and alpha-adrenergic agonists decrease cyclic 3′5′-AMP and increase mediator release. The augmented mediator release following cholinergic stimulation may also be mediated through increased cyclic 3′5′-GMP (Austen et al., 1975; Wassermann, 1977).

Mast cells release at least six different mediators, of which the three best known are histamine, slow reacting substance of anaphylaxis (SRS-A) and eosinophil chemotactic factor of anaphylaxis (ECF-A) (Wassermann, 1977). Although it is often assumed that these mediators cause many of the pathological changes in asthma, their exact role has not been defined. Apart from mediators released by mast cells there are probably other mediators such as prostaglandins and bradykinins acting on bronchial smooth muscle. Their role, if any, in asthma is also not clear.

Mucus production and mucociliary clearance

The ability to clear mucus adequately depends on the integrity of cilia and the amount and rheological properties of mucus. The tracer techniques used to assess mucociliary clearance present some problems in interpretation, particularly in patients with airways obstruction where the initial deposition of the tracer is disturbed. Care is therefore needed in predicting the clinical effects of drugs from these tests and the same is true for *in vitro* studies of mucus or sputum, which often correlate poorly with the clinical effects of the drug.

There is evidence to suggest that the intrinsic activity of cilia is increased by cholinergic agents (Kordik, Bülbring and Burn, 1952) whilst mucus production and mucociliary clearance are enhanced by both beta-2 adrenergic agonists and cholinergic agents (Wanner, 1977).

DRUGS AFFECTING AIRWAY CALIBRE

Anticholinergic drugs

The beneficial effects of inhaled belladonna infusions and smoking stramonium were appreciated well back into history and achieved a certain vogue in the ninteenth century. Anticholinergic drugs compete with acetylcholine on smooth muscle receptors and thus inhibit the bronchoconstricting action of the vagus. They probably also achieve their effects by reducing vagal influence on the mast cell and on mucociliary clearance, and this may explain why these drugs characteristically take about 60 min to achieve maximal bronchodilatation.

Parenteral atropine and hyoscine decrease airway resistance in normal subjects (Butler et al., 1960; Smith and Dubois, 1969) and in patients (Crompton, 1968), although both parenteral and oral atropine are associated with unacceptable side-effects for routine bronchodilator treatment (McNicol and Bruyns, 1964). When inhaled atropine was given in acute studies to patients with chronic bronchitis it caused comparable bronchodilatation to isoprenaline (Altounyan, 1964), whilst patients with asthma have usually responded better to beta-agonists than atropine (Altounyan, 1964; Crompton, 1968), although not invariably (Pierce, Allen and Campbell, 1979). The onset of action with atropine is slower than with isoprenaline and the maximum effect may not be seen for an hour. For this reason the two drugs were often combined to provide a rapid onset and prolonged action, but the popularity of these combinations has diminished with the introduction of longer-acting beta-agonists. Systemic anticholinergic side-effects from inhaled atropine occur infrequently, although dry mouth is common (Pierce, Allen and Campbell, 1979).

Ipratropium bromide has been introduced recently as a pressurized inhaler and may have less side-effects than atropine. It has shown some bronchial selectivity in animal studies (Bauer, 1975; Engelhardt and Klupp, 1975) and the poor absorption following inhalation further reduces systemic side-effects (Deckers, 1975). It again takes 60–90 min to achieve maximal bronchodilatation which then persists for up to 8 h (Ruffin, Fitzgerald and Rebuck, 1977). In patients with asthma it also appears to be less effective than a beta-agonist (Petrie and Palmer, 1975; Ruffin, Fitzgerald and Rebuck, 1977) although the combination of an anticholinergic drug with a beta-agonist may be more effective than either drug alone (Ruffin, Fitzgerald and Rebuck, 1977; Lightbody et al., 1978; Pierce, Allen and Campbell, 1979) (fig. 2).

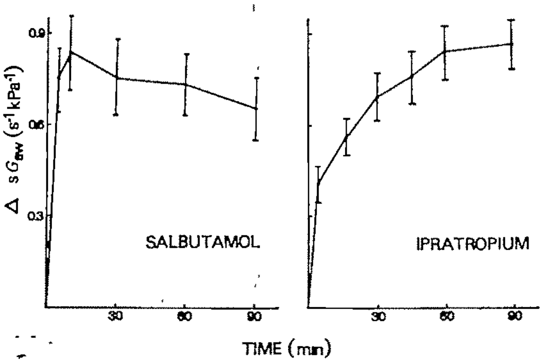

FIG. 2. Time course of the mean change in specific conductance of airway (s. G_{aw}) in normal subjects after salbutamol 200 μg (five subjects) and ipratropium 40 μg (eight subjects). Resting values of s. G_{aw} ranged from 1.27 to 1.93 s^{-1} kPa^{-1}.

Short-term comparisons with a beta-agonist in patients with chronic bronchitis have given inconsistent results with ipratropium, being less (Leitch et al., 1978), similar (Petrie and Palmer, 1975) and more effective (Poppius and Salorinne, 1973) than the beta-agonist. These discordant results reflect the problems of defining chronic bronchitis and how the patients are selected, the use of arbitary doses of each drug and the differing methods of assessing benefit. Further work is needed on the longer term effects of ipratropium in these patients.

Ipratropium provides some protection against exercise-induced asthma (Chan-Yeung, 1977; Thomson, Patel and Kerr, 1978), histamine inhalation (Harnett and Spector, 1976) and allergen challenge (Kersten, 1974). These studies do not necessarily imply vagal involvement in the bronchoconstrictor response, since all bronchodilating drugs will provide some non-specific protection to bronchoconstrictor challenges by virtue of bronchodilatation alone (Benson, 1975).

The reduction in mucociliary clearance in patients with chronic bronchitis following hyoscine (Pavia and Thomson, 1971) and i.v. atropine (Annis, Landa and Lichtiger, 1976) was not seen when ipratropium was taken in single large doses by normal subjects or in patients with mild chronic bronchitis (Matthys et al., 1975; Francis et al., 1977). Dryness of the mouth does occur, but other systemic anticholinergic side-effects are not seen, although it is not recommended for patients with untreated narrow angle glaucoma. The delay in achieving maximum bronchodilatation is a disadvantage to most patients.

Beta-adrenergic agonist drugs

Adrenaline used for many years as a bronchodilator was supplanted by the more specific beta-adrenergic agonist, isoprenaline. This in turn has been largely replaced by more selective beta-2 agonists such as salbutamol (fig. 2), rimiterol, terbutaline, fenoterol and, to a lesser extent, orciprenaline. It is generally assumed that the main effect of these drugs results from stimulation of smooth muscle beta-receptors, although part of their action may stem from effects on mast cells, mucociliary clearance or inflammation.

Isoprenaline came under suspicion as a possible cause of the increased mortality in asthmatic patients in the United Kingdom in the 1960's (Greenburg and Pines, 1967; Speizer et al., 1968) and although a cause and effect relationship was never proven, the consequent reduction in isoprenaline sales coincided with a reduction in asthma mortality (Inman and Adelstein, 1969). It was suggested that the non-selective beta-agonists might cause arrhythmia, particularly in hypoxic patients (Lockett, 1965; Collins et al., 1969), although there are several other possible explanations for the presumed association (Heaf, 1970). The possible safety benefit and the reduced frequency of side-effects has led to the widespread use of the more selective beta-2 agonists.

Isoprenaline and rimiterol are largely ineffective after oral administration because they are conjugated to an inactive form in the gut wall (Blackwell et al., 1974; Evans et al., 1974), a fate not shared by salbutamol, terbutaline and fenoterol, which are effective when given orally. Isoprenaline and rimiterol also have a short life after inhalation or i.v. administration as a result of O-methylation by catechol-O-methyltransferase (COMT). Salbutamol, terbutaline and fenoterol, resistant to breakdown by COMT, have a longer half-life and longer duration of action (Walker et al., 1972; Davies et al., 1974). There is little difference between the time course of salbutamol and terbutaline, but some evidence that fenoterol might have a slightly longer action (Beardshaw, Maclean and Chan-Yeung, 1974).

Inhalation of beta-agonists increases bronchial selectivity, since maximum bronchodilatation can be achieved with barely detectable blood concentrations and fewer side-effects (Walker et al., 1972; Larsson and Svedmyr, 1977). Inhalation is therefore preferable for routine use, with tablets reserved for patients unable to use an inhaler. The pressurized, metered aerosols are convenient and generally reliable when care is taken to ensure they are used correctly. Although there is concern about the long-term atmospheric effects of fluorocarbon aerosols, the danger to individual patients appears to be negligible unless the inhaler is grossly over-used (Dollery et al., 1970).

When normal subjects inhale from a pressurized aerosol less than 10% of the drug enters the small airways (Blackwell et al., 1974; Davies, 1975). With increasing airway obstruction this figure may be reduced and patients may also have more difficulty in co-ordinating their aerosol. In this situation somewhat greater bronchodilatation can be achieved with intermittent positive pressure ventilation (IPPV) (Choo-Kang and Grant, 1975; Cayton et al., 1978), although this was not shown to be of any greater benefit than quietly breathing the same solution through a Wright's nebulizer (Campbell et al., 1978). In fact, studies in patients with chronic bronchitis have shown less aerosol deposition in the lungs after

IPPV than after inhalation from an ultrasonic generator during quiet breathing (Dolovich et al., 1977). The newer lightweight nebulizers now available can be used with a face mask and may be particularly appropriate for young children (Bacon, 1978; Lenney, 1978).

In a severe attack of asthma beta-agonists can also be given by i.v. injection (Fitchett, McNicol and Riordan, 1975) or infusion and the relative merits of the i.v. and inhaled routes of administration are still debated. In one study of patients with severe asthma there was a good response to i.v. salbutamol 200 μg over 10 min after a poor response to inhaled salbutamol 5 mg given by IPPV (Williams and Seaton, 1977). A concurrent randomized trial of patients with equally severe asthma found the opposite; nebulized salbutamol 10 mg was slightly more effective than i.v. salbutamol 900 μg given over 45 min and the latter caused more side-effects (Lawford, Jones and Milledge, 1978). The differing results may reflect the superiority of nebulized aerosol to IPPV. Rimiterol can also be given by i.v. infusion producing comparable changes in FEV_1 and heart rate to salbutamol (Marlin and Turner, 1975). The shorter half-life could provide an additional margin of safety.

In status asthmaticus it is difficult to compare i.v. salbutamol with i.v. aminophylline, since these patients usually require concurrent treatment with steroids and inhaled drugs (Johnson et al., 1978). In clinical practice both drugs are usually given, i.v. beta-agonist with aminophylline suppositories or i.v. aminophylline with inhaled beta-agonist, in the hope that this will increase bronchodilatation with fewer side-effects.

The palpitations which occur with large doses of beta-2 agonists and smaller doses of the less selective beta agonists are caused both by cardiac beta-1 stimulation and indirectly by the reflex tachycardia and increased pulse pressure following the beta-2-mediated decrease in peripheral vascular resistance (Dunlop and Shanks, 1968). Tremor is also a common side-effect and, like the palpitations, tends to disappear if the patient continues with the drug, reflecting the development of tolerance or resistance (Larsson, Svedmyr and Thiringer, 1976). It has been suggested that excessive use of beta-agonists might produce similar resistance to their effects on the airways (Van Metre, 1969; Reisman, 1970; Connolly et al., 1971). This can be demonstrated in normal subjects (Holgate, Baldwin and Tattersfield, 1977), but so far it has proved difficult to confirm this prospectively in patients with asthma (Larsson, Svedmyr and Thiringer, 1976; Harvey and Tattersfield, unpublished observations).

Many patients show a small decrease in arterial oxygen tension following beta-agonists (Rees, Millar and Donald, 1967; Tai and Read, 1967). On average, this is about 3 mm Hg (0.4 kPa), but occasionally larger changes are seen which might be clinically important if the patient is not receiving additional inspired oxygen. This decrease is attributed to increased ventilation–perfusion mismatch following pulmonary vasodilatation in vessels previously constricted by hypoxaemia.

The metabolic changes observed with i.v. beta-agonists in normal subjects include increases in plasma free fatty acids, insulin, glucose and lactate concentrations (Goldberg et al., 1975). Patients with asthma have greater baseline concentrations of free fatty acids, insulin and glucose. The changes following beta-agonists have been variable although plasma, insulin and glucose can increase further and potassium will usually decrease (Leitch et al., 1976; Neville et al., 1977; Nogrady, Hartley and Seaton, 1977; Tickner et al., 1977). Diabetic ketoacidosis and lactic acidosis have been precipitated in susceptible patients (Leslie and Cotes, 1977; Thomas et al., 1977; Desir et al., 1978).

Alpha-blocking drugs

Single doses of alpha-blocking drugs cause bronchodilatation in patients with asthma (Patel and Kerr, 1975) and a reduction in exercise-induced asthma (Bianco et al., 1974; Beil and de Kock, 1978), although whether this is a result of alpha-blockade or the other pharmacological actions of these drugs is not clear. A long term study with indoramin showed little clinical benefit and many side-effects (Campbell and Dyson, 1977). If there is a place for alpha-blocking drugs in severe asthma, it has not been defined, and these drugs need to be used with caution in ill patients.

Theophylline drugs

Theophylline, a methyl xanthine, is not itself suitable for oral or i.v. use, but when combined with ethylene diamine as aminophylline can be given i.v. and with other modifications can be given orally or rectally (Paterson and Shenfield, 1974). After biotransformation in the liver it is excreted in urine (Paifsky and Ogilvie, 1975). There are variations between subjects in their ability both to absorb and to metabolize theophylline and this causes considerable problems. Slow release preparations provide more prolonged therapeutic blood concentrations than oral aminophylline, but they still cause quite large intersubject differences in theophylline blood concentrations (Waxler and Schack, 1950; Turner-Warwick, 1957; Boroda et al., 1973). Theophylline clearance studies after i.v. aminophylline also show considerable variations reflecting different rates of metabolism (Jenne et al., 1972). A small part of this can be predicted, since several studies have shown that clearance is increased in smokers and decreased in patients with pneumonia and heart failure (Hunt, Jusko and Yurchak, 1976; Piafsky et al., 1977; Powell et al., 1978). These variations are of particular importance for theophylline since the blood concentrations required for a therapeutic effect are close to toxic concentrations and in some patients they overlap (Yunginger et al., 1966; Mitenko and Ogilvie, 1973).

Steady state studies have shown that blood theophylline concentrations of 5, 10 and 20 μg ml^{-1} are associated with incremental improvements in pulmonary function, although some side-effects occur at 20 μg ml^{-1} (Mitenko and Ogilvie, 1973). Other workers have also associated side-effects with blood concentrations in excess of 20 μg ml^{-1} (Jenne et al., 1972; Nicholson and Chick, 1973). Many authors therefore aim for a blood concentration of about 10 μg ml^{-1} for a safe although submaximal therapeutic effect. Fixed i.v. regimes designed to achieve this (Mitenko and Ogilvie, 1973; Nicholson and Chick, 1973) can show a five-fold difference in blood theophylline concentrations, ranging from therapeutically inadequate to toxic values. A small improvement can be achieved by a slightly more flexible regime in which an allowance is made for factors such as smoking and pneumonia, but even so there is a wide range of blood concentrations, with some in the toxic range (Powell et al., 1978). Unless theophylline blood concentrations are monitored, the effects of treatment will be unpredictable.

The symptoms associated with theophylline poisoning have been reviewed in children admitted to hospital for this reason (McKee and Haggerty, 1957). Irritability, restlessness and tremor progressed to convulsions and coma and were associated with persistent vomiting and dehydration. As expected, the doses of theophylline causing these effects varied widely. Death can occur in patients receiving a single injection of aminophylline, sometimes as little as 100 mg. This is thought to be a result of the cardiovascular effects of aminophylline, since many of the reported patients were ill or had coronary heart disease (Merrill, 1943; Bresnick, Woodard and Sageman, 1948). It may also be a result of over-rapid injection, although this is difficult to document. A small decrease in arterial oxygen tension was noted after i.v. aminophylline as with isoprenaline, and again attributed to pulmonary vasodilatation (Rees, Millar and Donald, 1967).

It has been suggested that theophylline drugs and beta-agonists might have a synergistic effect on smooth muscle since both increase cyclic 3'5'-AMP by different mechanisms (Campbell et al., 1977). This is difficult to demonstrate conclusively in man without detailed dose–response studies. Intracellular synergy will not necessarily produce a synergistic response in measurements of flow or airway resistance, since the factors influencing these measurements are complex. In practice the combination of an oral theophylline and an oral beta-agonist produced only a small further increase in peak expiratory flow rate (Dyson and Campbell, 1977). The theoretical advantage of combining the two types of drug, whether the effect be additive or synergistic, is that the bronchodilating effect may be increased without an increase in side-effects. This would only be true for side-effects which were not common to both drugs and presumably not mediated through cyclic AMP.

Steroids

Although steroids are very effective in asthma, they only have a very small bronchodilating effect in normal subjects (Holgate, Baldwin and Tattersfield, 1977). Single-dose studies in stable asthmatic patients taking no other treatment showed a peak effect 5 h after i.v. hydrocortisone and 8 and 9 h after i.v. and oral prednisolone respectively (Ellul-Micallef, Borthwick and McHardy, 1974; Ellul-Micallef and Fenech, 1975). This delay of several hours is similar to that seen with steroids in other situations. Although this probably respresents the peak pharmacological effect, the maximum benefit to the patients often takes several days (Collins et al., 1975).

Steroids probably have several different actions, but their mode of action is still far from clear. Reduction of inflammatory mucosal swelling and oedema might be important in asthma (Baxter and Forsham, 1972). They are also known to potentiate the effect of beta-agonists in guineapig and human tracheal chains (Geddes et al., 1974) and in patients with chronic asthma not responding to isoprenaline (Ellul-Micallef, Borthwick and McHardy, 1974). Steroids also restore the airway response to salbutamol in normal subjects made tolerant or resistant to salbutamol by taking large doses (Holgate, Baldwin and Tattersfield, 1977). This potentiation of beta-agonists may be related to changes in the cell membrane, but is more likely to be mediated through intracellular mechanisms (Baxter and Forsham, 1972). Studies in other organs show steroid hormones binding with specific cytoplasmic receptors before entering the cell nucleus. Here they interact with chromatin, enhance messenger and ribosomal RNA and cause increased translation of proteins which then produce the observed hormonal effects (Feldman, Funder and Edelman, 1972). In airway smooth muscle this could lead to increased production of phosphorylating protein kinases which would then augment the response to cyclic AMP. The time course of 4–6 h in asthma is similar to that in other systems where there is more direct evidence for steroids acting through nuclear RNA, and it would fit with the fact that cyclic AMP concentrations do not appear to be increased by steroids (Baxter and Forsham, 1972).

It has been difficult to determine the correct dose of steroids for patients with severe asthma, since control studies are difficult and response is variable (Collins et al., 1970). A dose of 3 mg kg^{-1} every 6 h (200 mg for an average person) is usually satisfactory and when given by infusion will achieve plasma control concentrations greater than 100 μg dl^{-1} (Collins et al., 1975). High-dose corticosteroid regimes have not shown clear benefit and are more likely to cause side-effects such as hypokalaemia (Britton et al., 1976). Adverse bronchial reactions to i.v hydrocortisone have been reported in two aspirin-sensitive asthmatic patients, but this is extremely rare (Partridge and Gibson, 1978).

The introduction of inhaled steroid preparations has allowed many patients to reduce or stop regular treatment with oral steroids, although they may need oral or parenteral cover for exacerbations or surgery. There is little systemic absorption of betamethasone or beclomethasone after inhalation, so systemic steroid side-effects are not a problem with conventional doses. The only side-effects of note are an increased frequency of candida infection and occasional hoarseness.

Mediator antagonists

Drugs which antagonize the effect of mediators on bronchial smooth muscle might be expected to be of value in asthma. Most work has been done on oral and parenteral antihistamines which in adults have been ineffective, possibly because the dose required for bronchodilatation is greater than the dose producing side-effects, particularly drowsiness. In a recent study, an inhaled H_1-receptor antagonist, clemastine, caused bronchodilatation in a group of patients recovering from asthma (Nogrady et al., 1978) though this was not confirmed in a group of patients with stable asthma (Partridge and Saunders, 1979).

Drugs affecting prostaglandin synthesis, such as aspirin and indomethacin, have little or no effect in asthma apart from the very small proportion of patients who deteriorate, sometimes very rapidly, on exposure to small amounts of these drugs.

Drugs acting on the mast cell

The main action of sodium cromoglycate is to inhibit the normal degranulation of sensitized mast cells following antigen challenge, although it may also have membrane-stabilizing properties (Cox, 1967, 1971). Reaginic antibody still attaches to the mast cell, but mediator release is prevented. Since little absorption occurs after oral administration it is inhaled as a dry powder. The amount inhaled is reduced in patients with severe airways obstruction (Benson et al., 1973), but this is probably not too important since cromoglycate is a prophylactic drug to be taken regularly and not during an acute attack.

There has been difficulty in definining the place of cromoglycate in the treatment of adult asthma and there are considerable differences of opinion about its value. Some studies have documented improvement in pulmonary function (Robertson, Epstein and Warrell, 1969; Gebbie et al., 1972), whilst other patients under double-blind conditions have claimed improvement on cromoglycate in the absence of any change in spirometric tests (Howell and Altounyan, 1967; Bernstein et al., 1972). This may reflect the imperfections of tests such as the FEV_1 in assessing all aspects of asthma, but does suggest that the benefit overall is fairly small. Assessment is also complicated by an apparent continued effect from cromoglycate for a few weeks after the drug is stopped (Bernstein et al., 1972) and in some patients with an initial response to cromoglycate, a failure to deteriorate when the drug was replaced by a placebo after 1 year (Northern Brompton and MRC collaborative trial, 1976).

Cromoglycate has been of most benefit to atopic asthmatic children (Bernstein et al., 1972; Silverman et al., 1972) and in the prevention of exercise-induced asthma. The drug should be taken half an hour before exercise (Blackhall and Jones, 1969) and although a certain dexterity is needed to place the capsule in the inhaler, once prepared it can be used by most young children. Occasional patients with intrinsic asthma appear to benefit (Saunders, Rudolf and Brostoff, 1978), but the response is usually small. Side-effects are extremely uncommon apart from occasional coughing.

There has recently been a search for an effective oral anti-allergic drug and although many have looked promising, the results in clinical trials so far have shown them to be largely ineffective.

Mucolytic drugs

Drugs such as bromhexine and acetylcysteine cause impressive reductions in sputum viscosity *in vitro*, but their effect on mucociliary clearance is uncertain (Wanner, 1977). In clinical practice they have been disappointing.

Although beta-adrenergic agonists increase mucociliary clearance whilst anticholinergic drugs, apart from ipratropium, do the reverse, the clinical consequences of these changes still need evaluation.

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THE MANAGEMENT OF DIABETES DURING SURGERY

K. G. M. M. Alberti and D. J. B. Thomas

"Diabetes offers a serious bar to any kind of operation, and injuries involving open wounds, haemorrhage, or damage to the blood vessels are exceedingly grave in subjects of this disease. A wound in the diabetic patient will probably not heal while the tissues appear to offer the most favourable soil for the development of putrefaction and pyogenic bacteria. The wound gapes, suppurates, and sloughs. Gangrene readily follows an injury in diabetics, and such patients show terrible proneness to the low form of erysipelas, and cellulitis." (Treves, 1896.)

The advent of insulin revolutionized the treatment of diabetic patients undergoing surgery, a revolution that was extended by the discovery of antibiotics. Nonetheless, in unpractised hands surgery can still be disastrous for diabetics in terms of both morbidity and mortality. Even in good centres surgery carries a significant mortality and morbidity. Wheelock and Marble (1971) reported a 3.7% mortality in a series of 2780 patients studied between 1965 and 1969, while Galloway and Shuman (1963) had a 3.6% mortality and 17.2% morbidity in 667 cases. In the same period Alieff (1969) reported a 13.2% mortality. In diabetics undergoing renal transplantation there was two to four times the mortality compared with non-diabetics (Kjellstrand et al., 1972). The major causes of mortality and morbidity were and still are myocardial disease and infection. Obviously these are important in non-diabetics as well as in diabetics, but in the latter, poor control of diabetes with its attendant disturbances of electrolyte and intermediary metabolism will inevitably exacerbate these problems. Myocardial infarction itself is more likely to be mortal in diabetics (Soler et al., 1974) while resistance to infection is diminished in poorly controlled diabetes (Bagdade, Nielson and Bulger, 1972). Wound healing is also said to be impaired.

Diabetics undergoing surgery tend to be a high-risk group. Three-quarters or more of surgical diabetics are likely to be over the age of 50 (Galloway and Shuman, 1963). In this age group obesity is common and there is an increased prevalence of myocardial and peripheral vascular disease, as well as renal impairment, compared with the non-diabetic population. It is obvious from this that problems may arise both during and after operation in diabetics, and that these problems will be exacerbated by poor control of the diabetes. The magnitude of the problem for the anaesthetist and surgeon is demonstrated by the fact that it has been estimated that a diabetic has only a 50% chance of avoiding surgery during his lifetime (Root, 1966).

One further important point is that diabetes often presents *de novo* on surgical wards as a result of the stress either of the surgical condition or of admission to hospital. Beaser (1970) states that 25% of the diabetic patients on a surgical ward may be newly discovered cases. It is thus of paramount importance that surgical cases be screened adequately, as failure to make the diagnosis before operation may lead to a stormy postoperative course.

There is obviously a need for a logical straightforward set of guidelines for the treatment of diabetes during and after surgery. At present there are a multitude of recommended regimens, many of which are irrational if not dangerous. In the following review we shall first discuss the metabolic response of normal man to surgery and starvation (generally the fate of the surgical patient, wittingly or unwittingly) and how this may be modified in the diabetic patient. We shall then review some of the present regimens recommended for the treatment of diabetes in surgery. In the final section we shall discuss the rationale for the use of a simple i.v. regimen which can be applied to all diabetics undergoing surgery regardless of time of day or of severity of operation.

METABOLIC AND HORMONAL RESPONSE TO SURGERY

Metabolism in Normal Man

Fed and fasted states

In normal man anabolism and catabolism are finely balanced. During feeding anabolism predominates with the laying down of food reserves in the form of

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glycogen and triglycerides. At the same time protein synthesis is stimulated. During fasting, as for example during the night, the body switches to catabolism, mobilizing stored fuels. As starvation increases so the pattern of fuels used changes. During short-term starvation there is an obligatory requirement for approximately 180 g glucose per day for nervous tissue and red cell metabolism.

Some of the glucose need is met by mobilization of hepatic glycogen but reserves are relatively small, and a progressively greater proportion of the glucose requirement comes from gluconeogenesis. The major substrates for this are lactate and pyruvate, alanine, glucogenic amino acids and glycerol. Lactate and pyruvate are derived in part in extrahepatic tissues from circulating glucose and as such represent no net gain of glucose. However, a proportion also comes from muscle glycogen, thus creating a means, albeit energetically wasteful, whereby muscle glycogen can be converted into circulating glucose. Alanine is derived in muscle from the amino groups of other amino acids, in particular the branch chain amino acids, and pyruvate. Originally it was thought that the pyruvate was produced not only from glucose but also from the carbon skeletons of the other amino acids. There is now some doubt as to whether the latter occurs. If this is proved correct then no *net* gain of glucose can come from alanine, and other amino acids assume greater importance. These include glutamine which goes from muscle to gut, where it is converted to alanine and thence to the liver for gluconeogenesis. Regardless of the fate of the carbon skeleton there is a net flow of amino acids away from extrahepatic tissues with an overall loss of protein. Glycerol from adipose tissue lipolysis also acts as a glucose precursor, but quantitatively is unimportant.

In short-term starvation there is also increased lipolysis in adipose tissue. The released fatty acids are either used direct as a fuel or are converted by the liver to ketone bodies. These cannot be oxidized by liver and serve as a useful fuel in extrahepatic tissues. It should be remembered that, in resting man, 90% of the energy used by muscle comes not from glucose but from fatty acid and ketone body oxidation.

As starvation continues a major change, termed "ketoadaptation", occurs in nervous tissue. The brain starts to use ketone bodies and the overall glucose requirement decreases by 50%. Renal gluconeogenesis, which normally amounts to only 10% of the total, remains constant and hepatic glucose production decreases dramatically (Owen et al., 1969). Amino acid use for gluconeogenesis and for oxidation decreases at the same time, and urinary urea excretion shows a marked decrease, with ammonia assuming greater importance as a nitrogenous waste product (Cahill, 1970). During this period blood ketone bodies increase to concentrations of 4–6 mmol litre^{-1} from overnight fasted values of 0.05–0.50 mmol litre^{-1}. This is associated with a mild acidaemia.

The increase in ketone bodies and fatty acids has a further effect in inhibiting glucose oxidation in muscle and peripheral tissues, thereby preserving glucose and indirectly protein. This is the so-called glucose–fatty acid cycle (Randle et al., 1963). In terms of energy reserve triglycerides are much the most important with 15 000 g or 135 000 kcal in a 70-kg man. Liver glycogen amounts to only 100 g or 400 kcal, while protein can provide up to 25 000 kcal. Metabolism in starvation is, however, geared to protein preservation and the predominant fuel used is fat (Cahill, 1976). At the same time the basal metabolic rate decreases, which decreases the total caloric requirement.

All these processes are controlled through a delicate interplay between a group of hormones, the anabolic and catabolic hormones (table I). Only one

TABLE I. *Anabolic and catabolic effects of hormones.* + + = *major stimulatory effect;* − − = *major inhibitory effect;* +/− = *stimulation if insulin present, inhibitory if insulin absent;* (+) = *important only if insulin absent;* + ? = *selective stimulatory effect. No attempt has been made to indicate tissues where major actions occur. For further details see Alberti* (1979)

	Anabolic effects			Catabolic effects				
	Glycogenesis	Lipogenesis	Protein synthesis	Glycogenolysis	Gluconeogenesis	Lipolysis	Ketogenesis	Proteolysis
Insulin	+ +	+ +	+ +	−	− −	− −	− −	− −
Glucagon	−	−	0	+	+ +	(+)	+	0
Cortisol	+/−	+/−	− −	+/−	+	+	(+)	+ +
Catecholamines	−	0	0	+ +	+ +	+ +	+	0
Growth hormone	0	0	+ +	0	+	(+)	(+)	0
Thyroid hormone	0	0	+ ?	0	+	+	(+)	+

hormone has an overall anabolic effect and that is insulin. Secretion is stimulated by carbohydrate or protein feeding, or both. It is responsible for directing absorbed fuels into stores, such as glycogen, triglyceride and protein. At the same time it drives glucose into metabolically important tissues such as muscle and adipose tissue, simultaneously sparing other fuels and switching off lipolysis. In the liver, as well as driving lipogenesis and glycogenesis, insulin inhibits gluconeogenesis, even when present in small concentrations, thereby preventing unnecessary wastage of amino acids. One other hormone, growth hormone, has some anabolic effects, but these are all directed at protein preservation. Thus it inhibits glucose uptake by tissue such as muscle and simultaneously has a mild stimulatory effect on alternative fuel production, in the form of fatty acids and ketone bodies. Overall glucose utilization decreases, amino acids are spared and these are driven into cells and into protein synthesis by growth hormone.

The stress hormones, glucagon, cortisol and catecholamines, have combined actions which oppose those of insulin, but none alone has the importance and the unique properties as a catabolic hormone that insulin has as an anabolic hormone. Thus the main actions of cortisol are to cause net protein breakdown in extrahepatic tissues and increase the flow of gluconeogenic precursors to the liver, where it also enhances amino acid degradation and gluconeogenesis. Glucagon has its main effects on the liver, stimulating ketogenesis (when adequate amounts of fatty acids are presented), gluconeogenesis and glycogenolysis. It also specifically increases alanine uptake by the liver. In contrast, catecholamines act mainly on lipolysis and glycogenolysis.

Whether the reaction of the body is anabolic or catabolic depends on the relative amounts present of insulin and the other hormones. In the fed state insulin predominates, although glucagon and growth hormone secretion may increase as well. In starvation the concentrations of insulin slowly decrease, leaving a relative excess of the catabolic hormones and the body switches to catabolism, but in a finely tuned manner. Problems arise if there are sudden large increases in the concentrations of the catabolic hormones—and this is relevant to surgery and will be discussed below—or if insulin is absent as in the insulin-deprived juvenile-onset (Type I) diabetic. In this latter case the restraining effects of even basal concentrations of insulin are lost and catabolism runs riot. We have been able to demonstrate this experimentally in normal man by using somatostatin to inhibit insulin, growth hormone and glucagon secretion, and then selectively replacing or increasing the concentrations of the catabolic hormones (Alberti, Batstone and Johnstone, 1977; Johnston et al., 1979). This problem of total insulin deficiency is obviously of importance in the diabetic.

One hormone, triiodothyronine (T3), which is normally considered to be catabolic, and certainly increases the basal metabolic rate (BMR), shows interesting behaviour in starvation. In this situation concentrations of T3 decrease (and those of rT3 increase) as if in protection against excess caloric expenditure (Portnay et al., 1974) and this correlates with the decrease in BMR. This is also important with regard to nitrogen conservation as administration of T3 to starved subjects increases nitrogen excretion (Carter et al., 1975).

For further details on metabolic regulation in the fed and fasted states, see reviews by Cahill (1976), Newsholme (1976), Garland and Hales (1978), Söling and Seufert (1978) and Alberti (1979).

Response to surgery

Inevitably the fine regulation of metabolism described above is perturbed by surgery. Surgery provides one of the classical "stress" situations and the catabolic response to surgery and injury has been recognized for many years. In particular, it is characterized by increased metabolic rate, increased net protein breakdown with nitrogen loss and glucose intolerance. The extent of the metabolic disturbance is related to the severity of the operation (Allison, Tomlin and Chamberlain, 1969) and the presence of complicating factors such as shock and sepsis (Clowes et al., 1976). In uncomplicated elective surgery, particularly "superficial" operations, there is at most a 10% increase in basal metabolic rate and a very small increase in nitrogen excretion. The main changes will be present during operation, but will be short-lived thereafter. With more severe, complicated operations BMR may be doubled, protein wastage massive and the disturbance prolonged for many days.

The hormonal changes are well recognized (Johnston, 1974). First, there is increased catecholamine secretion and increased ACTH and cortisol secretion. These may indeed precede the actual operation and be a response to fear. There is a further increase during the actual operation, and an increase in plasma cyclic AMP concentrations (Gill et al., 1975). Glucagon (Russell, Walker and Bloom, 1975) and growth hormone secretion may also be increased, although some authors have found little or no change in glucagon (Giddings et al., 1976; Miyata, Yamamoto and Nakao, 1976). The exact stimulus which causes these increases is not clear. Obviously there is a strong central component and much of the endocrine disturbance, in particular with respect to glucocorticoids and growth hormone, does not occur or is at least modified by extradural anaesthesia (Nistrup-Madsen et al., 1977). The increased glucagon secretion will be contributed to by a direct effect of catecholamines on the pancreatic A cells.

Simultaneous with these changes there is marked inhibition of insulin secretion. This is present during operation, is associated with marked glucose intolerance and has been demonstrated by several authors (Allison, Tomlin and Chamberlain, 1969; Clarke, 1970; Wright, Henderson and Johnston, 1974). This is followed by increased insulin concentrations after operation but still associated with glucose intolerance. The suppression of insulin secretion during surgery is almost certainly a consequence of catecholamine inhibition (Porte et al., 1966).

These hormonal changes are associated with several interesting metabolic changes. Blood glucose concentrations increase during surgery, proportional to the severity and extent of the operation (Weddell and Gale, 1935; Hayes and Brandt, 1952). The increase in blood glucose persists after operation and this, with the hyperinsulinism that follows surgery, suggests a phase of insulin resistance. It was originally considered that extrahepatic glucose oxidation was decreased, but Long and colleagues (1971) showed normal or increased peripheral glucose oxidation. It is worth noting that insulin sensitivity may nonetheless be comparatively decreased as absolute concentrations of insulin are increased. The main defect, however, appears to be inappropriately enhanced gluconeogenesis (Giddings, 1974) which is non-suppressible by glucose (Gump et al., 1974). The cause of this phenomenon and the relative insulin resistance have not been clearly documented. Ross and colleagues (1966) could not correlate the insulin resistance with changes in cortisol and growth hormone concentrations and Clowes and colleagues (1976) have indeed suggested the presence of a "resistance factor" that they have called "lipid plasma A". It seems unnecessary, however, to evoke new factors. As outlined above, there is a complex interplay between different catabolic hormones and the combined increases in circulating concentrations of the different hormones probably account for the glucose changes, growth hormone and cortisol contributing principally in peripheral tissues, and glucagon, catecholamines and cortisol in the liver.

Changes in blood concentrations of gluconeogenic precursors have also been noted. After minor surgery there is little alteration in blood lactate and pyruvate concentration. However, increased concentrations are found after major operations (Schweizer and Howland, 1965; Thomas, Alberti and Platt, 1979, in preparation). This must be a result of increased extrahepatic production, as uptake for gluconeogenesis is simultaneously increased. The increased concentrations of catecholamines (Christensen, Alberti and Brandsborg, 1975) and cortisol (Alberti et al., 1977) are undoubtedly responsible, together with some inhibition of pyruvate oxidation. In some patients hypoxia or hypovolaemic shock, or both, will also contribute. Insulin resistance may contribute to impaired pyruvate oxidation (Ryan, 1976).

Fatty acid metabolites also show changes which are clearly distinguishable from those found in starvation. Interestingly, we and others have found that ketone body concentrations following surgery plus starvation are smaller than those found following starvation alone (Clowes et al., 1976; Foster et al., 1979). In our own patients this amounted to 2.94 ± 0.41 *v.* 5.68 ± 0.12 mmol litre^{-1} following a 72-h fast, rather greater than the values of 0.8 ± 0.02 and 2.0 ± 0.5 found by Clowes and colleagues (1976). The latter authors found even smaller values in the presence of sepsis. It can be calculated that utilization of ketone bodies and fatty acids as fuels by peripheral tissues decreases by 10% after uncomplicated surgery. Glucose use is not increased and the implication is that amino acids are being oxidized in increased amounts. This has been confirmed for branched chain amino acids (Ryan, 1976). The question arises as to the mechanism of the decreased fatty acid and ketone body availability. This is perhaps secondary to the increased insulin concentrations following surgery. Adipose tissue is much more sensitive than muscle to insulin and it is possible that, despite obvious insulin resistance in muscle, there is suppression of lipolysis and hence fatty acid and ketone body availability.

These observations fit in with the pattern of protein metabolism following surgery. It was originally assumed that there was increased proteolysis after surgery, but this probably only occurs in cases complicated by sepsis or shock. In uncomplicated cases protein breakdown appears normal but protein synthesis is impaired (O'Keefe, Sender and James, 1974; Crane et al., 1977; Williamson et al., 1977), although our own data do not support this (Foster et al., 1979). There are two possible mechanisms for this. First, as a result of increased branch chain amino acid oxidation, tissues may lack amino acids essential for protein synthesis. This has been suggested by Ryan (1976). Circulating concentrations of branched chain amino acids tend, however, to be increased (Dale et al., 1977) and Elia, Smith and Williamson (1979) have recently reported a block in tissue uptake of branched chain amino acids after operation. Linked with this is the observation that ketone bodies inhibit alanine output from tissues—an index of amino acid degradation—and it has been noted that severe injury is characterized by small ketone body concentrations and increased alanine values (Smith et al., 1975). The net results are a negative nitrogen balance and the relentless breakdown of tissue protein (although visceral protein tends to be protected) in the days following surgery.

These metabolic changes are also associated with changes in electrolytes. Sodium tends to be retained and intracellular concentrations increase while the reverse happens with potassium, with a resultant loss of potassium in the urine. At the same time there may be loss of calcium, magnesium and phosphate.

Many authorities have attempted to modify the catabolic response to surgery. Thus high protein feeding, amino acid infusions, growth hormone, and full parenteral nutrition have all been tried (Lee, 1974; Richards and Kinney, 1977). Of greatest interest in the present context is that insulin therapy in combination, obviously, with adequate amounts of calories and amino acids, is probably the most effective means available to date for reversing catabolism after operation. Allison and his group (see review in Woolfson, Heatley and Allison, 1977) have pioneered this therapy. Their findings emphasize the unique role of insulin as an anabolic hormone, and the predictable metabolic mayhem that will ensue if insufficient insulin is present. Their most recent report (Woolfson, Heatley and Allison, 1979) suggests that insulin is only really effective in the non-diabetic if the catabolic rate is increased.

Response to anaesthesia

So far all the emphasis has been on the metabolic response to surgery. Anaesthesia itself also has effects, although it has been suggested that waiting for anaesthesia has a greater metabolic effect than anaesthesia itself (Allison, 1971). Nearly all anaesthetics have some metabolic effects, with extradural and spinal anaesthesia having the least effects. This topic has been reviewed in detail many times (Greene, 1972; Petrides and Napp-Mellinghoff, 1978). Ether and chloroform have the greatest effects, causing hyperglycaemia, fatty acid mobilization and inhibition of insulin secretion, all secondary, presumably, to catecholamine discharge and ACTH secretion. The modern inhalation anaesthetic agents such as halothane have some effects, but these are minor compared with the stress of surgery itself (Allison, Tomlin, and Chamberlain, 1969; Clarke, 1970; Clarke, Johnston and Sheridan, 1970). There are also few metabolic effects of concern to diabetics of premedication or of muscle relaxants.

Metabolism in the Diabetic

It is obvious that if insulin is totally absent catabolism will predominate and death will ensue. Lipid mobilization is markedly enhanced; fatty acid release from adipose tissue increases; ketogenesis, spurred on by a relative excess of glucagon, accelerates and ketone body supply soon outstrips ketone body utilization with consequent ketoacidosis and severe acidaemia. Similarly, net protein breakdown occurs; gluconeogenic precursors flow to the liver; gluconeogenesis and glycogenolysis, freed from the usual restraint applied by insulin, are increased and hyperglycaemia occurs. This is exacerbated by the inability of muscle and adipose tissue to take up glucose. There is also an inappropriate increase in glucagon, cortisol and eventually catecholamine, all of which accelerate the development of hyperglycaemic ketoacidosis. This is followed by the well-known symptom complex of glycosuria, polyuria, dehydration, hyperosmolality and coma.

Electrolyte changes also occur with loss of sodium, potassium, calcium, magnesium and phosphate because of the diuresis. The loss of potassium is compounded by the acidaemia which drives potassium out of cells and the insulin deficiency which prevents normal intracellular accumulation of potassium (see Alberti and Hockaday (1977) for a more detailed account of the sequelae of insulin deficiency).

In milder insulin deficiency the predominant defect is failure of peripheral tissues to take up glucose properly. There is enough insulin present for control of adipose tissue metabolism and gluconeogenesis. The end result is hyperglycaemia with glycosuria, and some loss of electrolytes in the urine.

Effect of surgery in the diabetic

It is obvious from this account that surgery or a similar stress will tend to worsen the metabolic status in both insulin-independent ("maturity-onset", Type II) and insulin-dependent diabetics ("juvenile-onset", Type I). In the former, insulin demand will outstrip potential supply from the already compromised pancreas. The usual increase in insulin secretion after operation will not occur, so not only will insulin resistance be present but insulin deficiency will also result. This will lead to a greater impairment of muscle glucose utilization and more rapid gluconeogenesis; severe hyperglycaemia with hyperosmolality will thus ensue. This is obviously to be avoided. In minor surgery where the stress is small the perturbation will be short-lived if no additional therapy is given, but it is questionable whether even this is a permissible risk.

In insulin-dependent diabetes it is obvious that catabolism will predominate if the patient remains on a fixed dose of insulin before operation, with the same caloric input. In practice caloric input decreases to near zero and insulin requirements obviously decline, but again they do not decline to zero, and it is important to match the increased insulin requirement secondary to the stress during and after operation with the correct amount of insulin. Metabolic decompensation must be avoided, but so must hypoglycaemia.

TREATMENT OF DIABETES DURING SURGERY

Aims of treatment

The main aim of therapy must be to achieve rapid recovery from the surgical stress with a minimum of intercurrent problems related directly to the metabolic disturbance, such as ketoacidosis or hypoglycaemia, or those indirectly related such as infection, delayed wound healing or cardiovascular events. The main differences from therapy in the non-diabetic are the use of insulin and the choice of electrolyte and fluid replacement. It is beneficial, if not obligatory, for the diabetic, particularly those taking insulin or those about to have anything but the most minor surgery, to be admitted to hospital for assessment and stabilization of their diabetes at least 24–48 h before operation. If this were done universally morbidity and mortality (and overall hospital stay) would decrease sharply. Sadly this is not universal practice, because the point is often not appreciated and because of shortage of beds.

Insulin therapy for diabetics before, during and after surgery

Many different regimens have been suggested for the treatment of diabetes during surgery. Some of these are summarized in tables II and III. Different treatments have been proposed for Type I and Type II diabetics, for minor and major elective surgery and for emergency surgery. These will be discussed in turn. One of the major problems in assessing these regimens is that no large-scale prospective study of mortality, morbidity and metabolic status in which two or more regimens have been compared has been published. We have performed a small comparative study and results will be drawn freely from this (Thomas, 1978; Thomas, Alberti and Platt, 1979, in preparation).

Insulin-independent (Type II diabetics)

Table II shows some of the suggestions that have been made for the treatment of insulin-independent diabetics during surgery. If surgery is minor and the patient is on diet alone there is general consensus that no additional therapy is necessary, provided that the patient is well-controlled before operation. Glucose should be monitored after operation both in urine and in blood (see below for details). In patients taking oral antidiabetic therapy there is less general agreement. Older reports tend to suggest continuation of sulphonylureas up to the day before operation. On the day of operation no therapy is given. After operation, subcutaneous insulin may be given depending on urine or blood glucose concentrations.

More recently more emphasis has been given to insulin therapy with a change to insulin before operation often recommended, particularly if major surgery is planned. In view of the predictable metabolic sequelae of surgery, described in detail above, and including insulin resistance and negative nitrogen balance, this seems wise. We have compared the response to surgery of two groups of patients receiving sulphonylureas. Approximately half the patients received no therapy on the day of operation while the other group received insulin–glucose–potassium i.v. This comprised 10% glucose 500 ml containing potassium chloride 10 mmol and insulin 5 units (if blood glucose less than 6 mmol litre^{-1}) before operation) or insulin 10 units (if glucose greater than 6 mmol litre^{-1}). The infusion was given at 100 ml h^{-1} from 30 min before operation until the first oral food was taken. Blood glucose concentration remained stable in patients given the insulin infusion (table IV) while concentrations increased in the "no therapy" group by more than 5 mmol litre^{-1} from 30 min before operation to 4 h after operation. During this period blood glucose concentrations increased by

TABLE II. *Recommended regimens for the treatment of insulin-independent (maturity-onset) diabetes during elective surgery*

Author	Before operation	During operation	After operation
Malins (1968)	(1) Diet alone	(1) Nil	
	(2) Omit oral hypoglycaemic agents on day of surgery	(2) Nil	
		(3) Give insulin 10–20 unit s.c. + 50% glucose 50 ml before op. if control poor	Check blood-glucose. Maintain carbohydrate intake
Oakley, Pyke and Taylor (1968)	Omit therapy on day of operation	Nil	Give insulin if glycosuria present according to sliding scale
Beaser (1970)	Soluble insulin to improve control if necessary. Omit insulin or hypoglycaemic agent evening before op. Avoid long-acting agents	Nil	50% preoperative dose of oral agent for 2 days. Then glucose 50–75 g day^{-1} i.v. or orally. Supplementary insulin according to urine tests
Wheelock and Marble (1971)	Change patient's oral agents to isophane insulin if necessary (based on 24-h urine glucose). Else omit therapy	Nil or isophane insulin depending on therapy before op.	Glucose 100–150 g day^{-1} i.v. or orally. Give isophane insulin based on urine and blood glucose
Shuman (1971)	*Minor surgery*: Give usual dose of sulphonylurea. Withhold biguanides. I.v. glucose 150 g day^{-1} if necessary. Add soluble insulin 10 unit per litre of 5% glucose if blood-glucose high	Give insulin and glucose as pre-op if necessary	Give sulphonylureas. Add supplementary insulin s.c. according to urine tests
	Major surgery: I.v. insulin 10 unit per litre of 5% glucose	I.v. insulin 10 unit per litre of of 5% glucose	Continue i.v. insulin–glucose. Increase insulin to 16–20 unit litre according to urine glucose. Give supplementary insulin s.c. if necessary
Steinke and Soeldner (1975)	(1) Diet-treated patients. Nil	Nil	Observe closely.
	(2) Oral agent treated patients: change to isophane 10–20 unit day^{-1}	Isophane	Isophane + i.v. glucose. When oral feeding recommenced change to oral agents
Rossini and Hare (1976)	If blood glucose <150 mg dl^{-1} no therapy. If glucose >150 <250 mg dl^{-1} no change in therapy. If glucose >250 mg dl^{-1} give isophane 16–20 unit day^{-1}. If glucose >350 mg dl^{-1} give isophane 16–20 unit plus soluble insulin 10–20 unit day^{-1}	Nil, or 50% previous insulin as isophane	I.v. glucose + isophane if necessary
Petrides and Napp-Mellinghoff (1978)	(1) Diet. If post-prandial glucose <160 mg dl^{-1} leave therapy unchanged	Nil	Observe
	(2) Stop biguanides. Change from chlorpropamide to tolbutamide. Start i.v. tolbutamide 1 g in 5% glucose 500 ml + 5% fructose 1000 ml	Continue tolbutamide–glucose –fructose or no therapy for minor surgery	Continue i.v. if necessary. Restart oral agents with oral feeding

2.4 mmol litre^{-1} in non-diabetic controls. 3-Hydroxybutyrate values were extremely variable, but were nonetheless much smaller in the insulin-treated patients. Plasma non-esterified fatty acids (NEFA) showed a similar pattern. Concentration of lactate and pyruvate tended to be greater in the insulin-treated patients, presumably as a result of the effects of insulin, both inhibiting gluconeogenesis and at the same time causing increased extrahepatic lactate production from glucose. No symptomatic hypoglycaemia occurred.

Other parameters were also followed. Thus plasma potassium concentration tended to decrease in both groups but urea, perhaps reflecting protein catabolism, increased in the "no therapy" group, but decreased in the insulin infusion group.

Our conclusion was that it was sensible to use the insulin infusion regimen in all sulphonylurea-treated patients except for the well-controlled undergoing minor surgery. Other general guidelines are as follows.

Before operation all biguanides should be stopped because of their known tendency to enhance hyperlactataemia and to cause lactic acidosis (Alberti and Nattrass, 1977). Long-acting sulphonylureas such as chlorpropamide should be stopped at least 3 days before operation and the patient changed to tolbutamide or glibenclamide or, if poorly controlled, to a three-times-daily soluble insulin regimen. On the day of operation the insulin–glucose–potassium regime should be started at 8–9 a.m. If the operation is delayed there is no danger of metabolic decompensation. Once the patient resumes feeding, the infusion is stopped and the patient put on t.i.d. soluble insulin subcutaneously (8–12 unit per dose with further adjustments according to serial blood-glucose estimations) or, if surgery, and therefore the stress, was minor, oral hyperglycaemic agents can be resumed. Further details are shown in the Appendix.

Insulin-dependent diabetes

An equally large number of regimens have been proposed for insulin-dependent as for the insulin-independent diabetics (table III).

The "no insulin—no glucose" regimen has enjoyed some favour. In Fletcher, Langman and Kellock's early report (1965) an impressively small deterioration in glucose control was noted.

TABLE III. *Recommended regimens for the treatment of insulin-dependent (juvenile onset) diabetes during elective surgery*

Author	Before operation	During operation	After operation
Izzo (1965)	Stop long-acting insulins. Start on 6-hourly soluble insulin s.c. based on urine "sliding scale" with spot checks of blood-glucose 2 h after meals	Continue 6-hourly insulin based on "sliding scale". Give glucose as i.v. infusion. Use i.v. fructose for extra calories	Continue 6-hourly insulin based on "sliding scale". 10% glucose 500 ml or 5% glucose + 5% fructose 6-hourly. Change to oral feeding as soon as possible. When insulin requirements stable change to pre-admission insulin
Fletcher, Langman and Kellock (1965)	Usual therapy	Withhold insulin	Give soluble insulin s.c. according to "sliding scale" based on glycosuria
Malins (1968)	Control ketosis. Change to b.d. soluble insulin	Soluble insulin i.v. + glucose 25 g 2 h before operation	Check blood-glucose frequently, soluble insulin accordingly
Oakley, Pyke and Taylor (1968)	Control carefully	Omit insulin if well-controlled, give glucose 10–20 g i.v. if urine glucose free. In "ketosis-prone" give 50–70% usual morning dose of insulin 30 min before op. + 50% glucose 20 ml. For afternoon operations give 80–90% morning insulin s.c. + breakfast. Check blood-glucose in long operations—give insulin if glucose increases >100 mg dl^{-1}.	S.c. insulin + i.v. glucose depending on blood and urine tests
Beaser (1970)	75% usual total daily dose, all in morning or 25% usual total dose as soluble insulin with each meal	Give up to 25 units insulin in 5% or 10% glucose 50 g	Continue i.v. insulin in glucose; glucose 150–200 g day^{-1}. Supplementary s.c. insulin depending on blood- and urine-glucose

Continued on next page

TABLE III *Continued*

Author	Before operation	During operation	After operation
Wheelock and Marble (1971)	Stabilize on isophane or soluble + isophane	I.v. glucose 5% + 50% usual daily insulin dose s.c. Glucose 100–150 g on day of operation	Isophane b.d. ± soluble insulin. I.v. glucose if necessary—oral feeding as soon as possible
Shuman (1971)	Control	Usual dose of insulin morning of operation, 5% glucose i.v. containing electrolytes	If on isophane, increase dose slightly. Supplement with soluble insulin 6–20 unit based on blood- and urine-glucose
Steinke and Soeldner (1975)	Control on isophane or lente + supplemental soluble insulin	One-third usual total dose before op. as isophane, one-third after op.	Continue isophane. Supplementary soluble insulin if glycosuric or hyperglycaemic
Rossini and Hare (1976)	Stabilize carefully. If blood glucose 250–350 mg dl^{-1}, increase isophane insulin 10–20%. If blood glucose > 350 mg dl^{-1} add soluble insulin 10–20 unit	Give half total daily insulin as isophane a.m. and half immediately after op.	Give isophane with supplementary soluble insulin as before op. based on blood-glucose
Taitelman, Reece and Bessman (1977)	Control on isophane	Continuous i.v. insulin: 1 unit h^{-1} if preop. requirement $\leqslant$ 20 unit day^{-1}, 2 unit h^{-1} if preop. requirement > 20 unit day^{-1}. 5% glucose 500 ml/4 h	
Bacchus (1977)	Control	(1) I.v. 5% glucose in 0.9% saline + normal daily dose insulin as s.c. NPH or Lente. Immediate after op. 25% as soluble insulin s.c. (2) I.v. infusion of insulin in 5% glucose: soluble insulin 1 unit per 3–4 g glucose. Monitor blood-glucose concns	(1) 4–6 h post-op. 25% usual dose as soluble insulin s.c. depending on blood glucose (2) Continue i.v. infusion then change back to preop. therapy
Petrides and Napp-Mellinghoff (1978)	Control with intermediate or slow-acting insulins	Give 5–10% glucose infusion to make up usual calories, soluble insulin i.m. before op. according to blood-glucose	Immediately after op. measure blood-glucose 2–3 hourly, soluble insulin i.m. accordingly. 5% glucose 2–3 litre day^{-1}. Intermediate insulin + supplementary soluble insulin according to blood-glucose
Oakley, Pyke and Taylor (1978)	Soluble insulin b.d.	(1) Morning operations—omit breakfast and insulin (2) Afternoon operations—decrease morning insulin + breakfast. I.v. glucose at induction if blood-glucose low	5% glucose from time of operation. Soluble insulin with pump, 1–3 unit h^{-1}. Otherwise insulin 20 unit in 1 litre 5% glucose in 8 h. Continue until patient eating

Unfortunately, this gives a misleading picture of the metabolic status of the patient. The effect of starvation on an insulin-deprived diabetic is to cause a moderate decrease in blood-glucose concentration (Alberti et al., 1975). Simultaneously, blood ketone body concentrations increase sharply and acute metabolic decomposition begins with increases in plasma glucagon and cortisol concentrations. Because of the stress of operation, blood glucose concentration does not actually decrease with the "no therapy" regimen. Indeed, in our patients there was a 5.6-mmol $litre^{-1}$ increase in glucose (table IV). Ketone body concentrations were variable, but six of nine patients showed marked increases during and following operation (table V) and mean plasma NEFA increased significantly. In addition there was a marked increase

TABLE IV. *Blood-glucose concentration (mmol litre^{-1}) in normal subjects, insulin-independent and insulin-dependent subjects during and after surgery. Insulin-independent subjects were given either (a) an insulin infusion until the first meal or (b) no therapy until after the operation. Both groups received soluble insulin t.i.d. after operation based on plasma-glucose and "Dextrostix" readings. Preoperative therapy was reinstituted as soon as possible. Glucose was given as 5% glucose i.v. until oral feeding recommenced. Insulin dependent subjects were treated by one of four regimens. Groups (c) received insulin–glucose–potassium from 30 min before operation until normal feeding resumed. If operations were scheduled for the afternoon patients took breakfast with their normal insulin. Group (d) comprised four subjects from group (c) where the insulin–glucose–potassium infusion was continued for 72 h. Group (e) patients were given no insulin or glucose before or during operation. Groups (f) received half the usual morning dose of insulin s.c. together with glucose 25 g given i.v. over 4 h. *Samples taken 30 min after breakfast on the 1st, 2nd and 3rd days after operation. Results obtained at a District General Hospital and taken from Thomas, Alberti and Platt (1979). Number of subjects in parentheses. Results given as mean ± SEM*

	Before op.	15 min after induction	After operation				
			1 h	4 h	24 h*	48 h*	72 h*
Insulin-independent							
(a) Insulin infusion (9)	10.3 ± 1.1	11.6 ± 1.0	9.5 ± 1.1	10.1 ± 0.9	12.3 ± 1.2	11.9 ± 1.2	10.3 ± 1.3
(b) No therapy (11)	8.9 ± 0.8	8.8 ± 0.9	10.3 ± 1.1	14.2 ± 1.3	12.4 ± 1.1	12.7 ± 1.2	11.6 ± 1.8
Insulin-dependent							
(c) Insulin-infusion (short) (12)	9.1 ± 1.9	9.0 ± 1.8	8.8 ± 1.2	9.6 ± 1.3	12.7 ± 1.2	11.6 ± 0.8	6.3 ± 0.6
(d) Insulin-infusion (long) (4)	12.5 ± 3.8	—	—	14.1 ± 3.0	9.7 ± 2.0	7.8 ± 1.5	9.2 ± 2.2
(e) No insulin or glucose (10)	9.0 ± 1.1	8.7 ± 1.2	12.4 ± 1.6	14.8 ± 1.2	12.7 ± 1.3	14.7 ± 1.8	14.7 ± 1.8
(f) S.c. insulin + i.v. glucose (11)	9.3 ± 1.0	8.6 ± 1.3	11.3 ± 1.6	14.9 ± 1.2	13.9 ± 1.2	13.5 ± 1.2	17.3 ± 1.9
Non-diabetic (7)	5.1 ± 0.3	5.7 ± 0.5	6.8 ± 0.4	7.5 ± 0.4	7.0 ± 0.8	5.8 ± 0.2	5.0 ± 0.3

TABLE V. *Blood 3-hydroxybutyrate concentration (mmol litre^{-1}) in normal subjects, insulin-independent and insulin-dependent subjects during and after surgery. Groups and therapy as described in legend to table IV. Results are given as means ± SEM. Distribution of results was often grossly abnormal and this method of expression has been used simply for clarity*

	Before op.	15 min after induction	After operation				
			1 h	4 h	24 h	48 h	72 h
Insulin-independent							
(a) Insulin infusion (7)	0.21 ± 0.08	0.14 ± 0.08	0.02 ± 0.01	0.05 ± 0.02	0.03 ± 0.01	0.18 ± 0.11	—
(b) No therapy (9)	0.13 ± 0.04	0.20 ± 0.05	0.26 ± 0.07	0.25 ± 0.07	0.13 ± 0.06	0.08 ± 0.03	—
Insulin-dependent							
(c) Insulin infusion (short) (8)	0.24 ± 0.14	0.19 ± 0.04	0.11 ± 0.04	0.13 ± 0.04	0.13 ± 0.04	0.40 ± 0.29	0.30 ± 0.18
(d) Insulin infusion (long) (3)	0.13 ± 0.15	0.08 ± 0.02	0.13 ± 0.15	0.13 ± 0.13	0.05 ± 0.02	0.15 ± 0.10	0.24 ± 0.13
(e) No insulin or glucose (9)	0.40 ± 0.21	0.51 ± 0.23	0.57 ± 0.22	0.56 ± 0.17	0.43 ± 0.20	0.58 ± 0.30	0.44 ± 0.19
(f) S.c. insulin + i.v. glucose (8)	0.17 ± 0.07	0.19 ± 0.07	0.33 ± 0.17	0.58 ± 0.19	0.42 ± 0.20	0.50 ± 0.35	0.32 ± 0.19
Non-diabetic (6)	0.09 ± 0.04	0.15 ± 0.04	0.21 ± 0.06	0.33 ± 0.07	0.19 ± 0.13	0.08 ± 0.03	0.27 ± 0.21

in plasma urea concentration and urine urea excretion during the day before operation and the first day after operation. There were also markedly negative potassium, phosphate, calcium and magnesium balances. This should emphasize the need to examine parameters other than glucose when assessing the efficacy of a regimen.

Other suggested regimens advocate giving a fraction of the usual dose of insulin as a subcutaneous bolus followed by an infusion of i.v. glucose. We have found little benefit of such a regimen (tables IV and V) compared with no therapy at all. Undoubtedly reasonable results have been achieved with many of these regimens, but most of them are based on habit and practice rather than logic.

Since continuous i.v. insulin therapy was introduced for the treatment of diabetic ketoacidosis (Page et al., 1974) there has been a resurgence of interest in the use of this type of therapy in all diabetic emergencies (Leslie and Mackay, 1978). Many groups now use continuous insulin infusion for the treatment of diabetics during surgery, but few proper studies have been reported. Taitelman, Reece and Bessman (1977) compared results obtained with their usual therapy or two-thirds of the usual dose of isophane insulin subcutaneously with a regimen in which insulin 2 unit h^{-1} was given continuously with 5% glucose 125 ml h^{-1}. Patients usually receiving isophane 20 unit per day or less were given insulin 1 unit h^{-1}. The patients were undergoing elective orthopaedic operations. Control of blood-glucose was better on the insulin infusion regimen than on isophane insulin, but it should be noted that two patients out of eight receiving 2 unit h^{-1} showed rapidly decreasing blood-glucose concentrations. Woodruff and colleagues (1977) using a 1-unit h^{-1} regimen also showed reasonable glycaemic control, but stopped the infusion 1 h after the end of operation.

We have looked at two regimens with continuous insulin infusion. In the first the infusion was commenced 30 min before operation and was as described above (insulin 2 units – glucose 10 g – potassium 2 mmol per hour) and continued until the first oral feeding. In four patients the infusion was continued for 72 h. In the main group, glucose control was improved over the "traditional" therapies up to 4 h after operation (table IV) and ketone body concentrations were decreased. In the group with a 72-h infusion, glycaemic and ketone body control was improved for the whole 72 h compared with all other groups. It is important at this point to distinguish between the apparently poor prognostic sign of a low ketone body response to surgery in non-diabetics (Smith et al., 1975; see above) and the control of ketosis in a diabetic by the use of insulin. In the latter case insulin has beneficial effects on protein metabolism as well as on carbohydrate and lipid utilization. The so-called protein-sparing effect of ketosis as popularized by Blackburn and colleagues (1973) is irrelevant in the diabetic patient. We noted, indeed, that plasma urea concentrations decreased and that calculated nitrogen balance in the infused patients was more positive than, not only "traditional" therapies, but the non-diabetic group as well. Similarly, plasma potassium concentration remained stable and potassium balance was considerably improved compared with other regimens. Clinical episodes of hypoglycaemia did not occur, although periodic adjustment to the insulin infusion rate was made with the rate increasing to 10 unit h^{-1} in one extremely ill, infected patient.

Our recommendation would be to use the insulin infusion regimen in all insulin-dependent diabetics undergoing any form of surgery. The insulin dose can be adjusted according to blood-glucose measurements. Continuation of the infusion until the patient is eating normally would seem desirable, at which time a return can be made to the preoperative insulin regimen. Alternatively, the patient can be treated with a Soluble or Actrapid or Leo Neutral insulin regimen starting at 12–16 units t.i.d. with further doses based on blood-glucose concentrations.

Method of administration of insulin

I.v. infusion of mixtures of glucose, insulin and potassium have been used clinically for nearly 20 years (Sodi-Pollares et al., 1963). The first major advocants for its use in surgery were Galloway and Shuman (1963), although they tended to reserve it for milder cases. One main argument about the use of insulin infusions concerns the method of delivery. Sönksen and colleagues (1968) and Weisenfeld and colleagues (1968) both showed clearly that insulin adsorbs to glass, with the latter authors finding the same for plastic tubing. This has led many authorities to reject the use of insulin added to standard i.v. solutions. The problem can be obviated by adding albumin, polygeline (Kraegen et al., 1975) or a small volume of the patient's own blood (Sönksen, 1976) to the infusion. Alternatively, it has been suggested that flushing the giving-set with 25–50 ml of the insulin solution in the infusion bag prevents further loss (Petersen, Caldwell and Hoffman, 1976). We found 72–90% insulin recovery from a glucose–potassium–insulin mixture of the composition used in our treatment regimen. This was considered clinically acceptable.

The alternative is to use a concentrated solution of insulin in a small volume. This may be done using an infusion pump with a plastic syringe. Taitelman, Reece and Bessman (1977) reported 90% recovery of insulin with this system and it has been advocated for therapy after surgery by Leslie and Mackay (1978) with insulin at a concentration of 1 unit ml^{-1} in saline 0.154 mol $litre^{-1}$. An interesting recent development is the use of the pump to infuse insulin 0.5 unit h^{-1} i.v. in patients not otherwise receiving i.v. therapy and having relatively minor procedures. Excellent preliminary results have been obtained (Barnett, Pyke and Watkins, personal communication). In well-staffed centres where care before and after operation is meticulous, insulin infusion with a pump is the treatment of choice, but even so Leslie and Mackay reported two pump failures. In our own District General Hospital we felt strongly that the insulin and glucose infusions should not be divorced. I.v. infusions from bags often run at varying rates, or stop altogether, while infusion pumps can occasionally fail. By combining insulin and glucose in the same infusate we feel that the added safety, in the average hospital and recovery ward, more than compensates for the somewhat variable loss of insulin through adsorption.

Recently, publications have appeared in which a glucose-controlled insulin infusion system (the so-called artificial endocrine pancreas) has been used to control diabetes during and after surgery (Pfeiffer et al., 1976; Schwartz et al., 1979). This is an ideal system, in that normoglycaemia can be maintained throughout regardless of i.v. fluid replacement and surgical manoeuvres. However, it is costly, as yet a research tool, and in the majority of cases quite unnecessary.

Monitoring insulin therapy

The keystone of all forms of management of diabetes during surgery is measurement of blood-glucose concentration. Urine glucose measurement is retrospective with a long time delay and is too insensitive. It provides information on whether blood-glucose concentrations are increased, but when values are negative does not distinguish between severe hypoglycaemia and values just below renal threshold (9–12 mmol litre^{-1}).

Ideally, blood-glucose concentrations should be measured before operation, once or twice during the operation (depending on the duration of surgery) then 2–3-hourly after operation until the patient is feeding again or at least until the morning after operation. Thereafter 3–4-hourly measurements are required if the patient continues to be fed i.v. It is vital that results should be available rapidly. In many hospitals 4- or 5-h delays in reporting results occur, and this is unacceptable. If a speedy service is not available then a rapid method should be available for use on the ward. Sophisticated apparatus such as the Yellow Springs Analyser, which can be used with whole blood, are advisable for this purpose but are expensive and susceptible to clinician abuse. Careful use of Dextrostix or Reflotest with a reflectance meter is more than adequate for surgical purposes. The new cheaper forms of reflectance meter, such as Glucochek, seem ideal and should be within the budget of all surgical units. It cannot be emphasized too much that proper staff training is required if these machines are to give accurate results.

The following simple guidelines can be used to modify insulin therapy if blood-glucose measurements are available. If blood-glucose before operation is less than 6 mmol litre^{-1}, start with insulin 5 unit per 500 ml of 10% glucose + potassium 10 mmol. If the value increases to more than 10 mmol litre^{-1}, double insulin content. If glucose value before operation is more than 6 mmol litre^{-1}, start with insulin 10 units per 500 ml of glucose. If in any subsequent measurement the value is greater than 10 mmol litre^{-1}, replace infusion with insulin 15 units per 500 ml of glucose and 20 unit if blood glucose is greater than 20 mmol litre^{-1}. Occasionally, further increases may be necessary. Halve the dose to 5 unit/500 ml if there has been a decrease to less than 5 mmol litre^{-1}. In practice, frequent adjustment is unnecessary after the acute phase when, on average, 4 unit h^{-1} were needed following major operations. It is worth noting that this regimen uses more glucose than that of Taitelman, Reece and Bessman (1977), with which rapidly decreasing glucose concentrations were noted in two of eight patients given insulin 2 unit h^{-1}.

It is pertinent to mention so-called "sliding scales" for insulin administration based on urine-glucose. These are used as security blankets by the nervous or ignorant. Their use encompasses comforting numerical guidelines, but they are based on false logic. The limitations of sliding scales in patient management are manifold. First they are always retrospective. This may be harmless in a stable situation, but after surgery blood-glucose concentrations can change sharply. A patient may thus have urine containing 2% glucose (because blood-glucose was high some hours previously) at a time when blood-glucose concentrations are near normal or decreasing rapidly. Second, urine may not be available at the desired time, which in many wards would mean that no insulin was given at all. Third, urine volumes and glucose thresholds may change after surgery. *In toto*, the effect of using sliding scales is often to induce glycaemic instability of roller-coaster proportions.

Factors influencing insulin requirement

Many factors may influence requirement during and following surgery. Awareness of these may pre-empt possible problems in metabolic regulation. Obviously the stress of surgery induces some degree of insulin resistance and this is proportional to the severity of surgery. The hormonal basis for this has been described above. Infection also may cause a dramatic increase in insulin requirement. This is probably caused by increased glucagon (Rocha et al., 1973) and cortisol (Beisel et al., 1967) secretion. Approximately 13% of Galloway and Shuman's series (1963) had infections, with similar figures reported by Beaser (1970), so that infection is not an uncommon complication after operation. In particular, urinary tract infections should be sought and treated.

Several drugs may increase insulin requirement including steroids, catecholamines and propranolol. In addition it should be remembered that infusion of blood increases insulin need in that, even when glucose content is small, contents of lactate and pyruvate are high and these precursors will stimulate gluconeogenesis, particularly in diabetics. One final and common situation in which additional insulin may be needed is that of the obese patient. Such patients are classically insulin-resistant as a result of "down regulation" of insulin receptors. If diabetics are more than 50% heavier than ideal body weight it is advisable to double the usual insulin dose and even greater amounts may be necessary.

Intravenous fluids and electrolyte replacement for diabetics during and after surgery

So far we have considered only the use of 10% glucose as an i.v. replacement fluid for diabetics. "Normal" saline (0.154 mmol litre^{-1}) has no particular hazards for the diabetic, but one or two commonly used replacement fluids such as Hartmann's solution are less desirable. We have noted a sharp increase in blood-glucose concentration in diabetics when given Hartmann's solution during or after operation (Thomas and Alberti, 1978). This may be caused by the lactate component being converted readily to glucose. Other lactate-containing solutions should also be avoided. If alkalinization is desired there seems little objection to bicarbonate.

Fructose administration has enjoyed intermittent favour in the treatment of diabetics after operation (Halmagyi and Israng, 1968; Mehnert, 1970). It is metabolized rapidly to glucose and lactate, with the latter predominating. If the circulation is compromised or there is abnormal liver function, lactic acidosis may ensue (Woods and Alberti, 1972).

Potassium therapy has been referred to above. Moderate replacement, together with i.v. insulin infusion, results in only small total body losses compared with most other treatment regimens. In the longer term significant decreases in plasma phosphate and magnesium occur with surgery, and replacement should be considered if patients have prolonged periods of i.v. alimentation after operation.

Emergency surgery and diabetes

Diabetics are as likely to require emergency surgery as the rest of the population: 5% (33) of Galloway and Shuman's operations (1963) in diabetics were of this type. Eighty per cent of these were the result of infection. In such cases we again would use the glucose–insulin–potassium infusion. If initial assessment indicated co-existent diabetic coma, precoma or severe metabolic decompensation, then surgery should be delayed until the metabolic status of the patient has improved. This is particularly true for conditions associated with severe abdominal pain, as this may be caused purely by the ketoacidosis and disappear completely with appropriate treatment of the ketoacidosis (Campbell et al., 1975). The converse is also true, however; that is, severe peritonitis may be present with minimal pain, perhaps as a result of autonomic neuropathy (Wheelock and Marble, 1971). This is exceedingly rare.

Postoperative complications in diabetics

Diabetics may develop any of the usual complications after operation. The commonest relate to infection (see above) which must be sought assiduously and suspected in any patient showing an increased insulin requirement after operation.

Cardiovascular complications. A disproportionate number of operations in diabetics are for cardiovascular disease—either myocardial, or of the legs. In such cases diffuse disease is almost always present. In a series of 100 diabetic patients undergoing lower limb surgery for gangrene or infection Kahn, Wagner and Bessman (1974) noted cardiac disease in 63%, peripheral vascular disease in 44% and cerebrovascular disease in 24%. There was a 9% mortality with six of the deaths caused by myocardial infarction. Higher mortality rates have been reported by others (Ecker and Jacobs, 1970).

Lower limb amputations are still unfortunately common in diabetics. In 1968 Warren and Kihn found that half of their major lower limb amputations were performed on diabetics. Undoubtedly this figure can be improved upon with intensive education and care, but cases still occur with distressing regularity. The overall outcome is poor in diabetics, as shown for example for transmetatarsal amputations by Effeney and Lim (1977). Similarly, when major vessel grafting is undertaken results are poorer in diabetics than in non-diabetics. LoGerfo, Corson and Mannick (1977) found a 72% graft patency after 5 years in their group as a whole, but only 45% in diabetics. Similar experiences occur with cardiac surgery.

In lower limb surgery the situation is complicated by the presence of microvascular disease and neuropathy as well as large vessel disease. In the myocardium there may also be small vessel disease (Ledet et al., 1979). The presence of this diffuse vascular disease affecting both small and large vessels undoubtedly contributes to the morbidity and mortality of diabetics undergoing surgery for any cause.

Other problems specific to diabetes. A significant number of diabetics coming to surgery will have some degree of renal disease. Hypertension, oedema and proteinuria should be sought. If diabetic nephropathy with clinical sequelae is present, special care must be taken with respect to parenteral feeding, and the use of drugs which are normally excreted in the urine.

The other major symptom complex likely to afflict diabetics is neuropathy. Somatic neuropathy should not complicate general surgery. However, autonomic neuropathy can present real problems. A neuropathic bladder can present with retention after operation. Postural hypotension may also cause problems. The most dramatic of the probable complications attributable to autonomic neuropathy has been pointed out recently by Page and Watkins (1978). They reported 12 episodes of sudden cardiorespiratory arrest, three of which occurred during anaesthesia, in patients with severe autonomic neuropathy. They suggested that arrests were caused by respiratory rather than cardiovascular causes. Anaesthetists should be alerted to this possibility and proper assessment of autonomic nervous function performed before operation in all long-standing diabetics.

CONCLUSIONS

In conclusion, much has been written in the past on surgery in diabetic patients, but there are few objective reports and comparisons of the different recommended regimens. Many of these are complicated and invite error. We have used a regimen which we have found safe, simple and easy to manage in an average hospital. This involves the i.v. administration of insulin, glucose and potassium as a single infusion. This is commenced from the morning of the day of operation and continued until normal feeding is reinstituted. The regimen is applicable to insulin-independent and insulin-dependent diabetics alike. Problems with severe hypoglycaemia or hypokalaemia have not been encountered and positive benefits with respect to blood-glucose stability, and nitrogen and potassium balance have been noted. Frequent monitoring of blood glucose is necessary for all regimens but can be achieved with simple bedside methods. In well-staffed centres insulin can be given with more precision and less adsorptive losses using an infusion pump. The increase in insulin requirement after operation, caused by infection and certain drugs, has been emphasized. Finally, the possibility of morbidity or mortality from cardiovascular causes should be remembered.

APPENDIX

GUIDELINES FOR CARE OF DIABETIC PATIENTS DURING AND AFTER OPERATION

(A) *Maturity-onset diabetics: minor operations*

Assuming well-controlled; if not change to insulin preoperatively and treat as in (C).

(i) *Before operation.* If on a long-acting sulphonylurea (e.g. chlorpropamide) change to tolbutamide or glibenclamide 1 week before operation. Stop all biguanides.

(ii) *During operation.* No sulphonylurea on day of operation. Treat as non-diabetic if blood-glucose < 7 mmol litre^{-1}. Check blood-glucose before operation and 4 h after operation.

(iii) *After operation.* Recommence sulphonylurea with first meal. Use i.v. glucose with caution, if at all.

(B) *Maturity-onset diabetics: major operations*

If badly controlled, change to insulin and treat as in (C).

(i) *Before operation.* As for (A) above.

(ii) *During operation.* As for insulin-dependent diabetics (see below).

(iii) *After operation.* As for insulin-dependent diabetics (see below). Once the patient is eating, treat with t.i.d. Actrapid or Leo Neutral insulin—about 8–12 units before each main meal is a rough starting guide, but more will be needed in those who are obese, are infected, have hepatic disease or are receiving steroids. The dose should be adjusted as necessary, and once it decreases to less than 20 units per day, transfer back to oral agents or diet.

(C) *Insulin-dependent diabetics: all operations*

(i) *Before operation.* Stabilize as carefully as possible for 2–3 days before operation. All patients should be on at least twice-daily insulin (e.g. Actrapid and Retard, Soluble and Isophane.) On the day preceding operation give short-acting insulin only (i.e. Actrapid, Soluble or Leo Neutral t.i.d.).

(ii) *During operation.*

a. Give *no* subcutaneous insulin on day of operation, even if the surgery is planned for the afternoon (although this should be avoided if at all possible).

b. Set up an infusion of 10% glucose 500 ml containing Actrapid or Leo Neutral insulin 10 units plus KCl 1 g at 8–9 a.m. Run through in 4–5 h.

c. Check blood-glucose and plasma potassium before infusion and after 2–3 h. If the latter blood-glucose is between 5 and 10 mmol litre^{-1} then continue the infusion as before. If the blood-glucose is outside this range, change the insulin as follows:

If glucose <5 mmol litre^{-1} change to 10% glucose 500 ml+insulin 5 units+KCl 1 g.

If glucose >10 mmol litre^{-1} change to 10% glucose 500 ml+insulin 15 units+KCl 1 g.

If glucose >20 mmol litre^{-1} change to 10% glucose 500 ml+insulin 20 units+KCl 1 g.

d. Thereafter check blood-glucose 2–4-hourly using Dextrostix, preferably with the aid of a Reflectance Meter or Glucocheck machine. N.B. Meticulous technique is required if useful results are to be obtained —in particular ensure that the Dextrostix are not old or discoloured. If bedside machines are not available then read the "stix" by eye. If the value by this method is less than 6 mmol litre^{-1} or greater than 11 mmol litre^{-1} send a sample to the laboratory for accurate measurement.

e. Continue to adjust insulin and potassium doses according to results (e.g. if plasma $K^+>4$ mmol litre^{-1} then stop the KCl, if plasma K is <4 mmol litre^{-1} increase to 2 g per 500-ml bottle).

(iii) *After operation*

a. Continue with 4–5 hourly infusions of 10% glucose–insulin–potassium, checking blood-glucose 4-hourly, and plasma K^+ 8-hourly. If fluid needs to be restricted for any reason, then equivalently smaller volumes of 20% or 50% glucose can be used, though these should be given via a central line.

b. Stop infusions when oral feeding is recommenced, and give t.i.d. Actrapid or Leo Neutral (daily total dose to equal the normal preoperative dose, adding an extra 20% if infection is present, and an extra 20% if the patient is receiving steroids).

c. Adjust dose as necessary and return to original preoperative regimen (i.e. short-acting/long-acting insulin combination) in 2–3 days.

d. If oral feeding cannot be restarted 48 h after surgery, consider parenteral nutrition.

(D) *Intravenous fluids*

These can be as for non-diabetics, except that lactate containing fluids should be avoided.

Special Notes

Cardiac operations. Note that patients on cardiac by-pass receive considerable extra glucose from the "deadspace" of the machine. In such patients insulin 20 units per 500 ml of 10% glucose should be used as soon as they are put on by-pass . If volumes need to be restricted 50% glucose 100ml or 20% glucose 250 ml are equivalent in glucose content to 10% glucose 500 ml.

Sepsis. Sepsis will always greatly increase insulin requirements.

Continuous therapy. If the infusion stops, the patient's extracellular fluid will contain no effective insulin within *30* min. Therefore ensure that treatment is *continuous.*

Normoglycaemia. Aim to maintain blood-glucose between 5 and 10 mmol litre^{-1}. The only possible benefit of a greater concentration is an osmotic diuresis.

Common sense. These are guidelines. The starting regimen (glucose 500 ml+insulin 10 units+KCl 1 g) is based on experience and a comparative study, but it is not meant to be unthinkingly adhered to. Patients will always vary, so therapy must be flexible and common sense applied.

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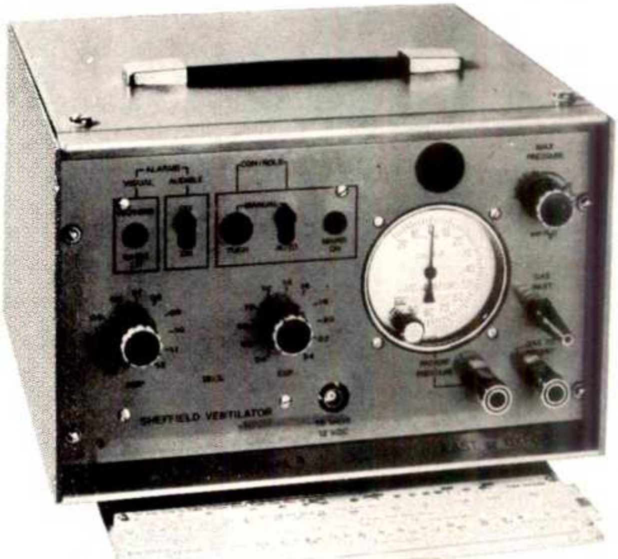

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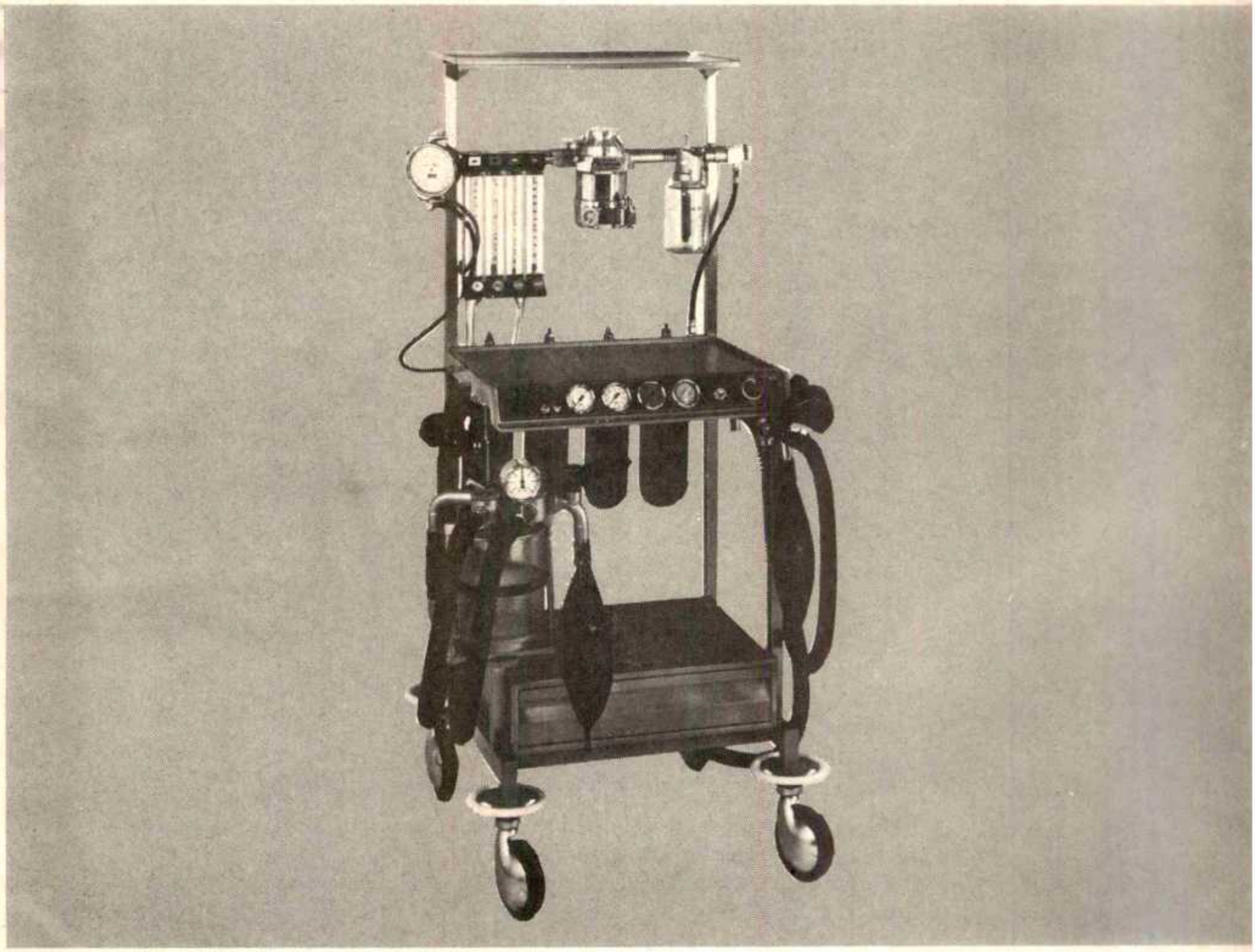

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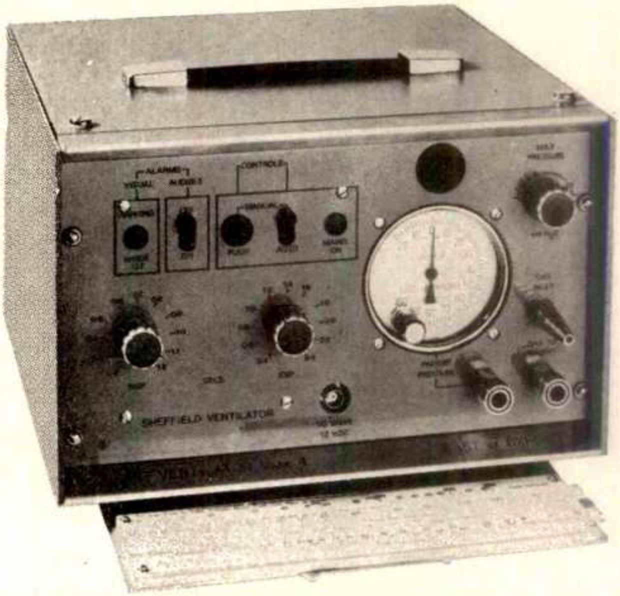

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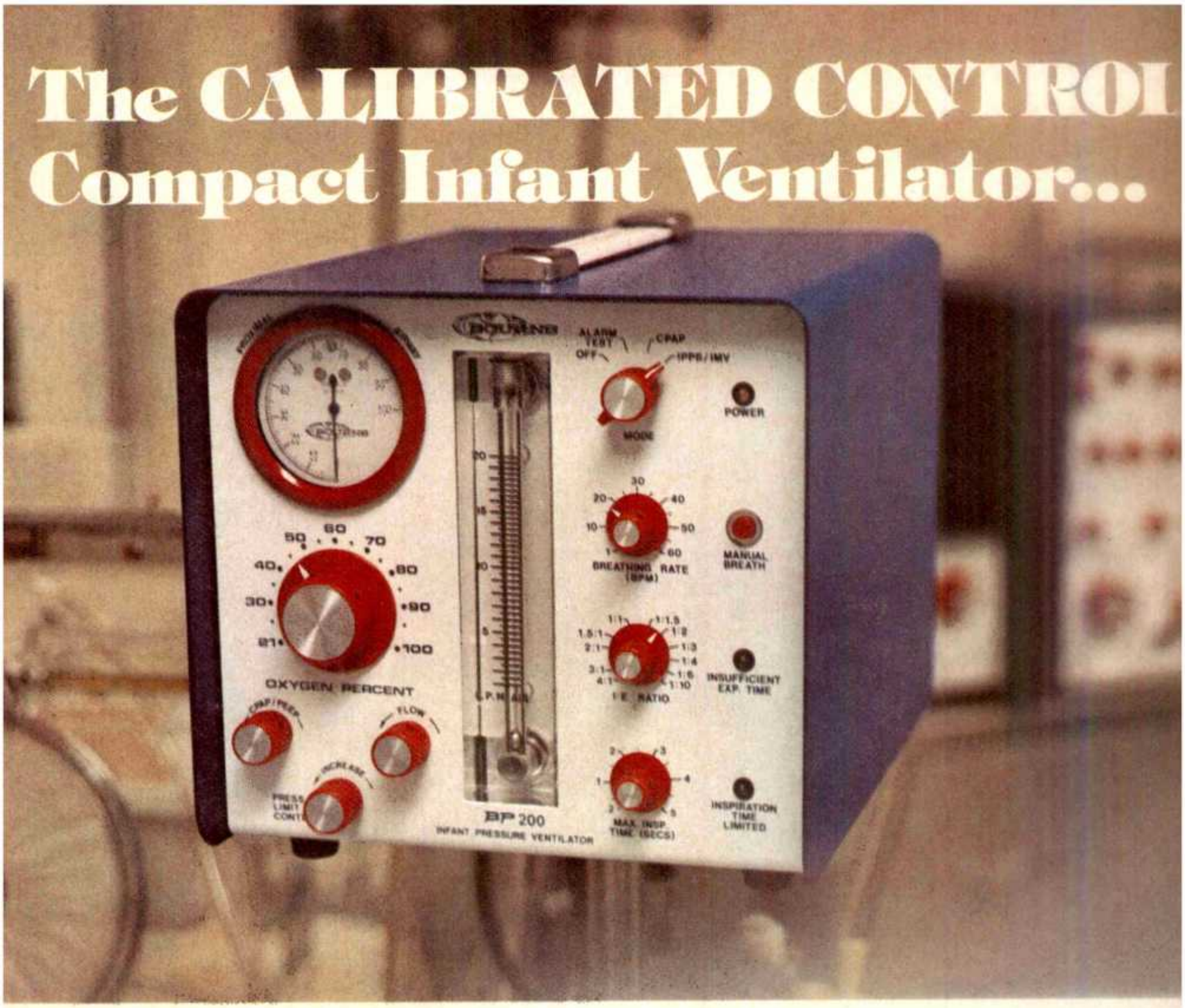

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Proposed Programme of Symposium on Dental Anaesthesia

Friday 19th October 1979 from 9 a.m.–4 p.m.

Venue: London Zoological Society Meeting Room, Regent's Park

" Dental Anaesthesia "

Chairman: Dr V. A. GOLDMAN

"The Sitting Position": Mr D. C. RULE
"The Supine Position": Professor M. HARRIS
"Patient Assessment and Selection": Dr T. E. MCEWAN

DISCUSSION

"Anaesthetic Agents and Methods"

Chairman: Dr P. J. VERRILL

"Inhalational Methods": Dr J. V. I. YOUNG
"Inhalational Agents": Professor L. STRUNIN
"Intravenous Agents": Dr T. M. SAVAGE
"Diazepam": Dr A. P. RUBIN
"Relative Analgesia": Mr W. A. ALLEN

DISCUSSION

"Should Dental Practitioners give General Anaesthetics ?"

Chairman: Dr P. J. VERRILL

Panel: Professor J. S. ROBINSON, Professor J. A. THORNTON, Dr V. A. GOLDMAN
Speakers: Mr P. SYKES, Dr P. J. TOMLIN
"If things go wrong . . .": Dr J. D. K. BURTON

Details from:

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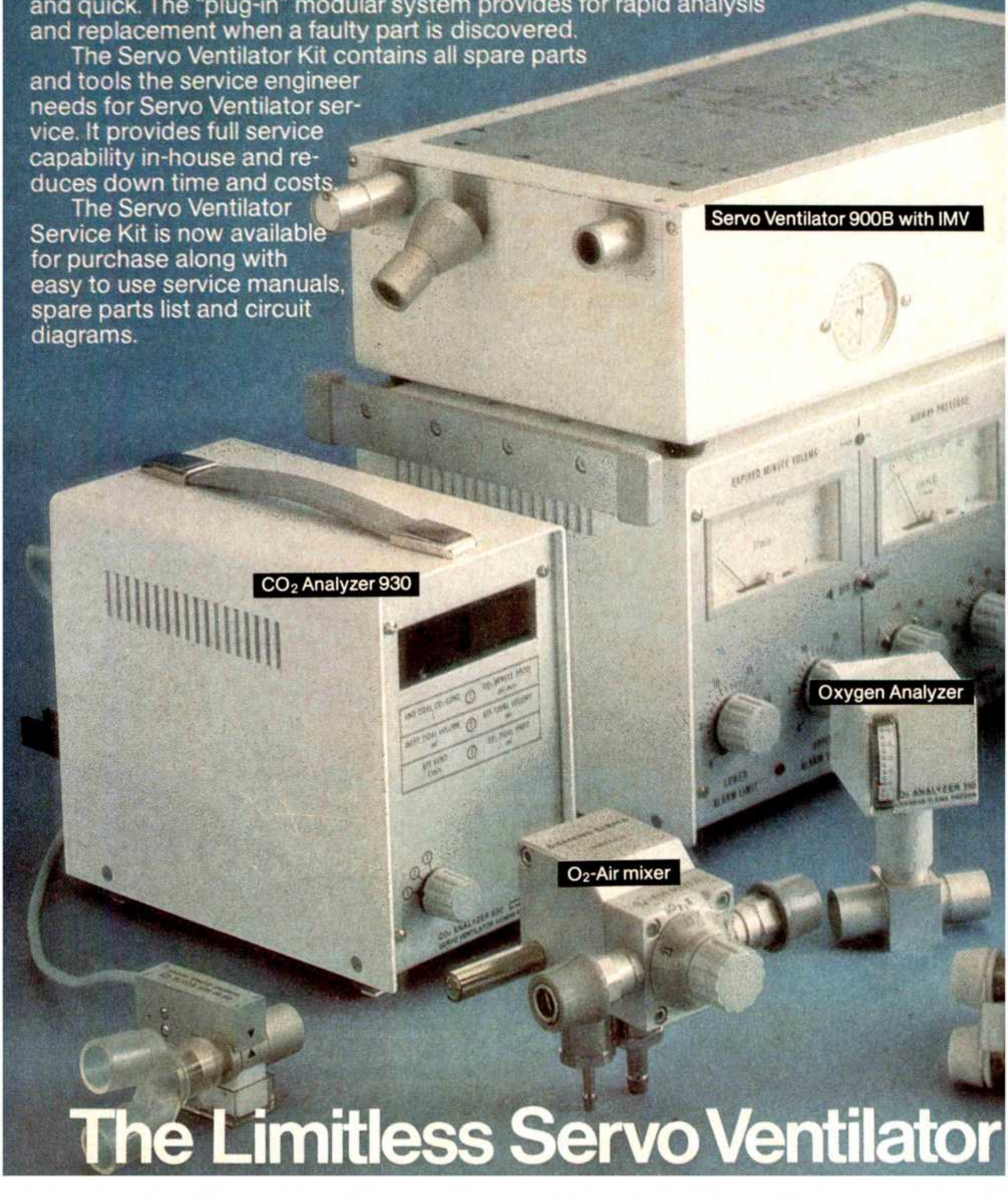
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Summary
Introduction (not headed)
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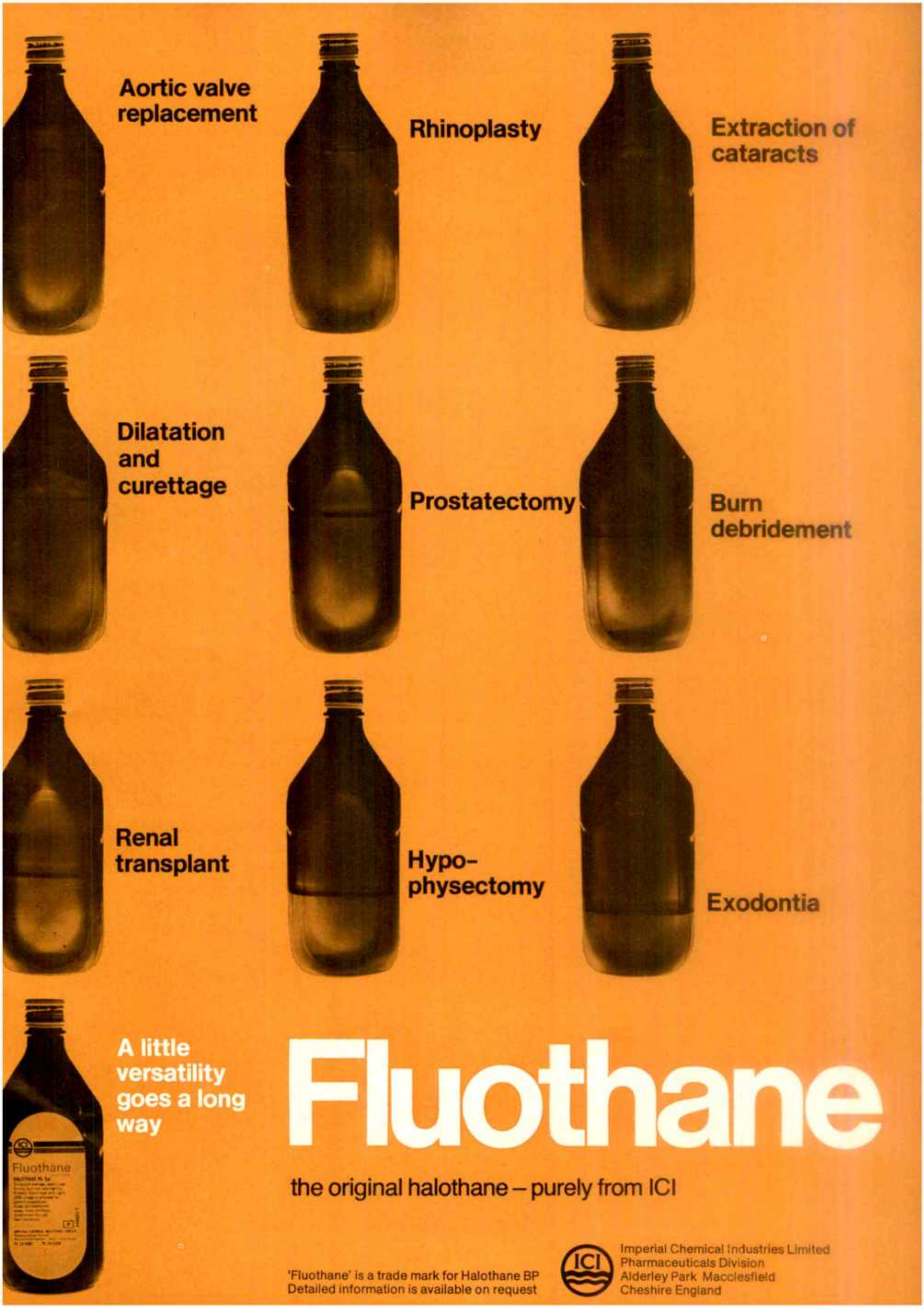

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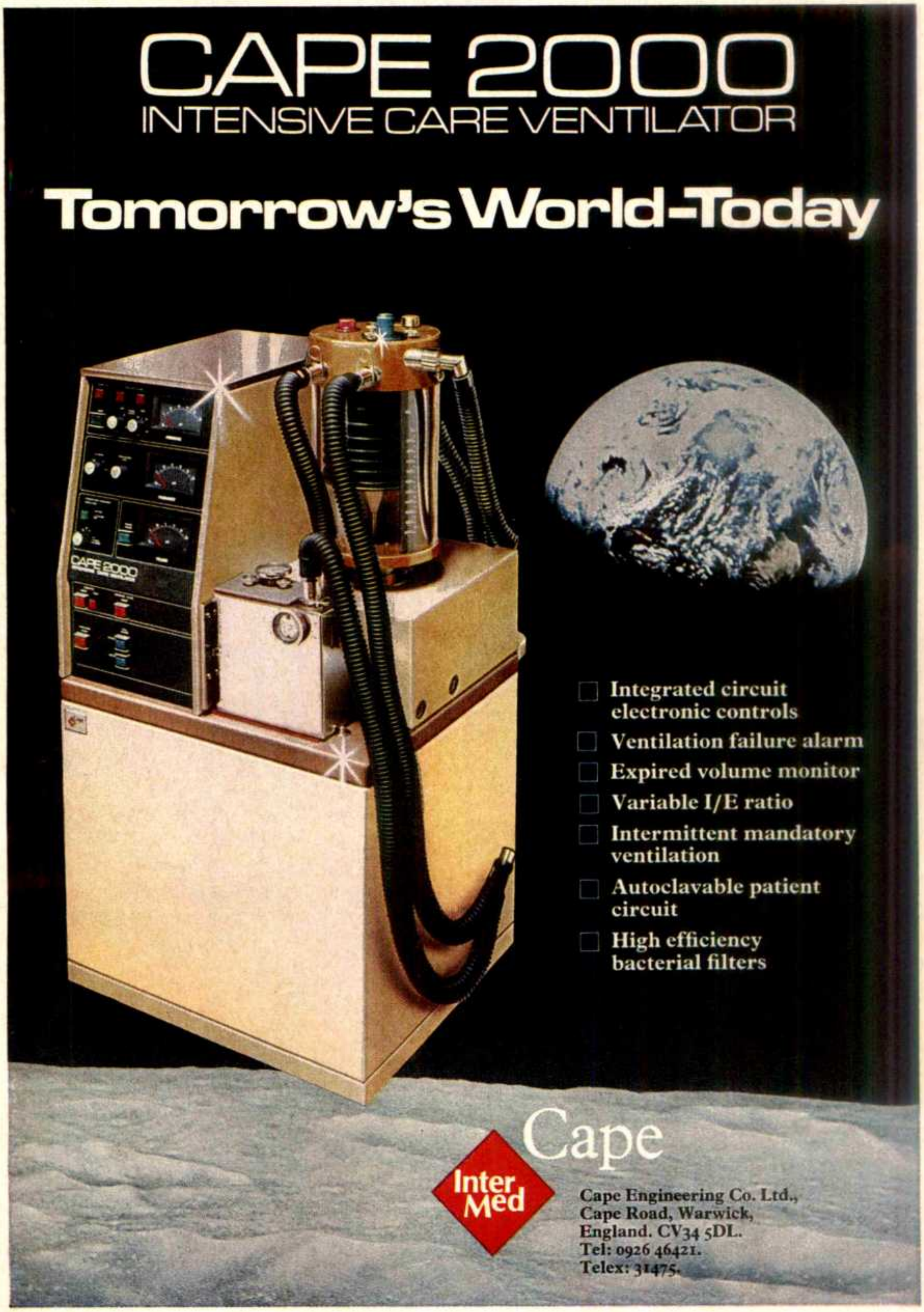

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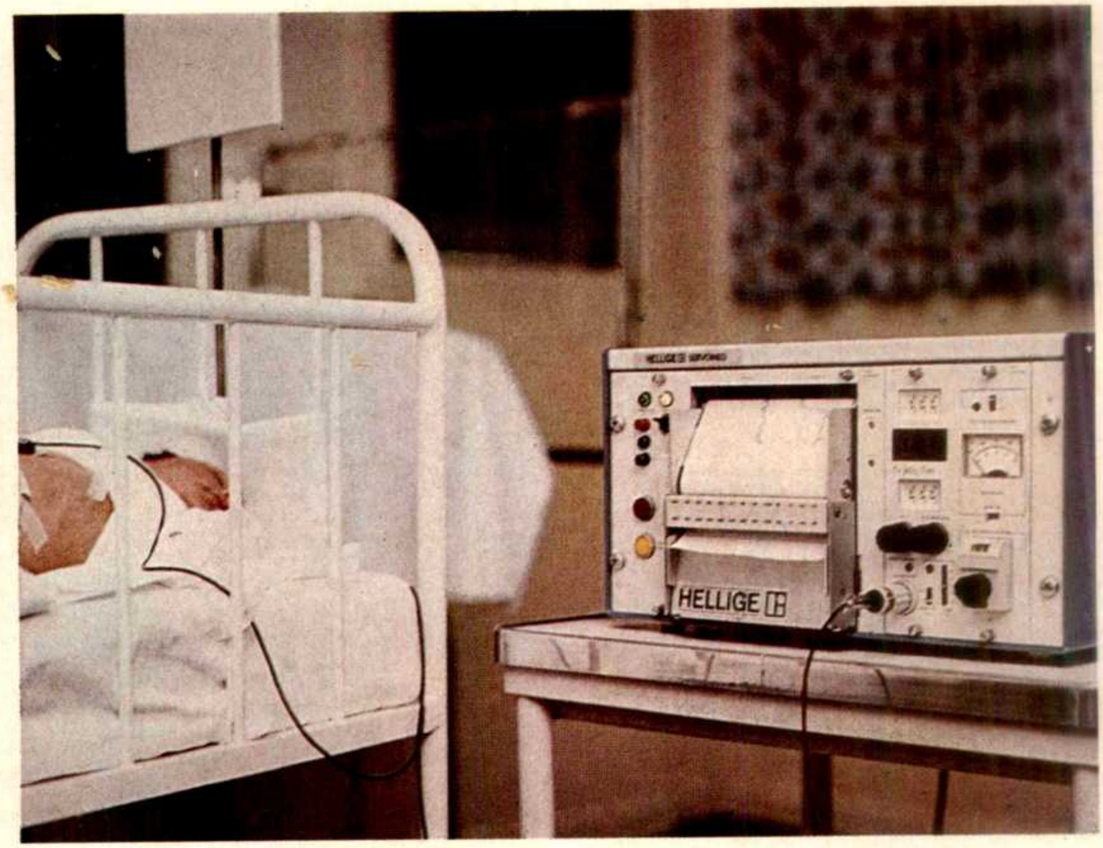

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Managing Editor: A. Doenicke, München, Chirurgische Universitäts-Poliklivik, Anaesthesie, Pettenkoferstr. 8a, D-8000, München 2

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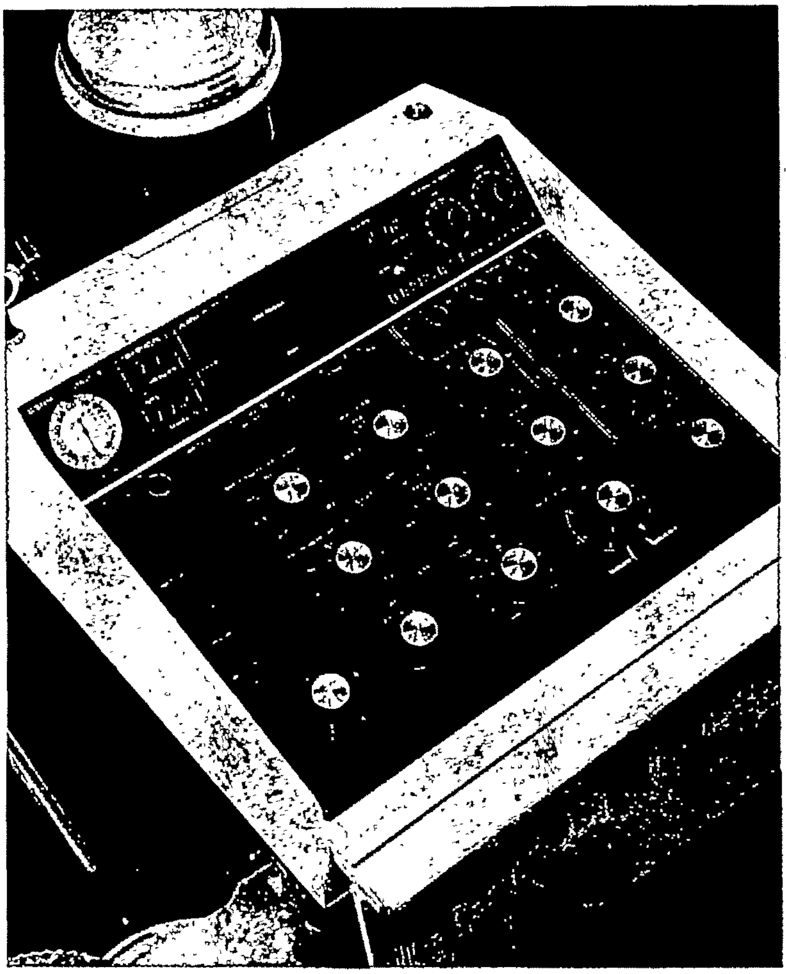

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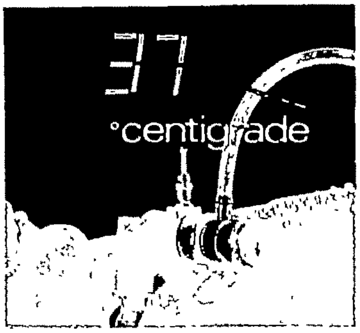

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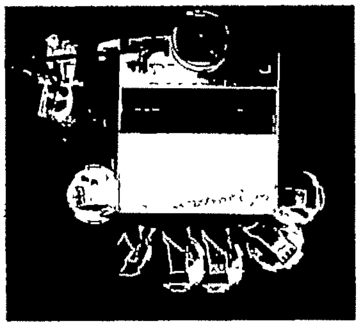

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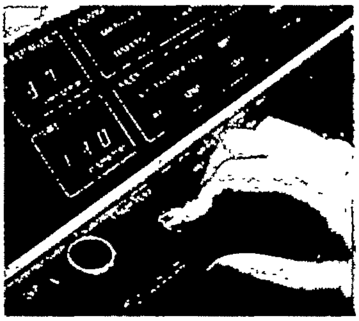

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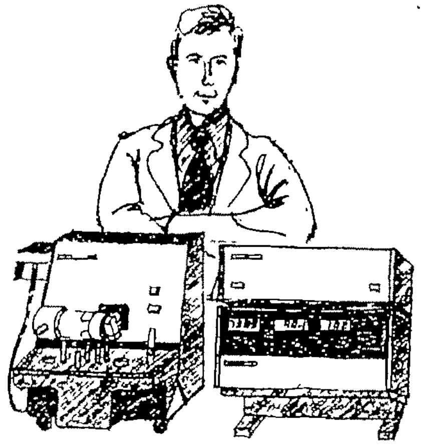

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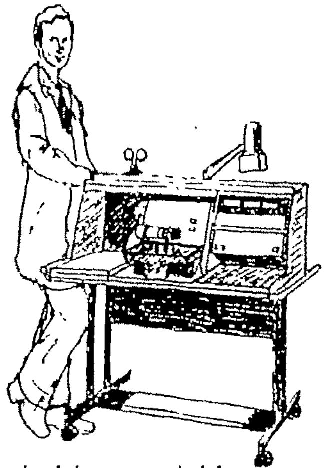

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EDITORIAL

ON BEING AWARE

The following are the unedited recollections of a medically qualified lady who experienced Caesarean section under general anaesthesia which was insufficient to prevent awareness during part of the procedure

I went unconscious very suddenly—literally as though someone had switched the lights out. I have no memory of the intubation. After a gap of uncertain (though fairly short) time (from 2 to 5 minutes) I gradually became aware of a mental haze in front of me, which I was automatically trying to clear. After probably 2 minutes, the haze evaporated and I was left in a still, silent limbo. I was profoundly confused. I did not know who or where I was, or what on earth was happening (I was in exactly this state following the first GA). This relatively happy state was interrupted by a voice in the space above me (some remark about my bladder) and I instantly understood my predicament: that I was lying there intubated, covered in green towels, my abdomen split open, strange people delving inside me, blood, swabs on the rack, etc.

My first reaction to this was an irrational surge of fear and panic and the absolutely desperate necessity to move. I felt I had to insert some of my own will on the situation. The closest parallel I can think of is of being in a coffin, having been buried alive. It was only then that I realized I didn't have a body to move. I searched for my feet, and couldn't find them. I nevertheless made a massive effort to move my non-existent right foot—I didn't realize that I had succeeded until a voice about 10 feet away (i.e. near my feet) said: "She's moving her toes, it's time you got her to sleep". I immediately realized that what I had done was to invite more pancuronium, and I made no further attempt to move (until after the pain started). I somehow felt I should conserve any power to move that I still had.

I remained in this state-of-mind (horizontal and supine) but otherwise totally dissociated, without any body image; continously filled with fear, listening to every word, every sound in the theatre, quite *compos mentis* and fully appreciating my position. One pint of beer would have dulled my mind more than the "anaesthetic". The only difference from my normal thinking was that I had slight difficulty in initiating thought (this wore off during the time I was awake—? an effect of the thiopentone). I felt constantly guilty, as though I were eavesdropping on the conversation above me. Also my first reaction to any event was rather childish—followed by an accurate intellectual appraisal; e.g. after several minutes I suddenly felt a cold strip of something from my left eye to my left ear—I thought "You mustn't cry, they'll think you're a baby if you cry... Oh! it's all right, you're only lacrimating because you're light."

Every sensation which intruded into my emptiness seemed to startle me; I couldn't see, so I had absolutely no warning of what was coming.

Of course, I heard the baby crying. "There's a baby crying (how odd, in theatre!) Oh!—it's *my* baby." I am ashamed to say I felt absolutely no emotion at this (such was my fear and terror) only a mild relief that I had been able to understand a small part of what was a totally alien and incomprehensible situation. There followed a confusion of sound and half-heard words—I am sure I didn't lose any of my consciousness—I just didn't seem to manage to catch what the nurses were saying.

Very suddenly I had the most horrible sensation down the back of my throat—as if rough fingers were marching down my throat—and I felt my pharynx gagging in response. "What's that?—oh, it's only the nasogastric tube—I'm going to be sick, I'm going to be sick." After a few seconds I stopped gagging and it all vanished (nasogastric tube and pharynx) and I was left, as before, with only my mind and my hearing. Strangely, now that my attention had been drawn to my throat, I was aware of a gentle dragging on the right side of my mouth—in no way unpleasant and not intruding as a "sensation", it was just there when I thought about it.

Soon after this, someone pulled my right forearm towards my face (in order to facilitate inserting a retractor). This was most strange; I suddenly possessed my right arm and was surprised to find it was lying bent on my chest. I felt the pressure of the fingers and heard paper rustling very near to my ears. The fingers disappeared and, as soon as my arm stopped moving, it too was gone.

Immediately following this there came three rough stripes across my abdomen. I would guess from anterior superior iliac spine to anterior superior iliac spine, from left to right. This feeling was unpleasant though not actually painful, as if someone had a strip of sandpaper and was drawing it across my flesh, pressing down very hard. I still can't work out what this was. Almost before the third stripe had finished, it was followed by the pain—as suddenly as though I had been stabbed. It was situated exactly in the centre, just above the symphysis pubis (as far as I could tell). This was the first pain I had felt during the operation and once it had started, it stretched continuously into the period of amnesia. It was bad from the onset, and it increased in severity. In character it was exceedingly unpleasant. The nearest comparison would be the pain of a tooth drilled without local anaesthetic—when the drill hits a nerve. *Multiply* this pain so that the area involved would equal a thumb-print, then pour a steady stream of molten lead into it. If you imagine the effect of a too-hot pan moved from the cooker on to a plastic surface, then that is what that pain was doing to my non-existent body. Searing, melting, pressing me into the table—with the nasty reminder of a dentist's drill. It never stopped, or wavered in intensity, except in becoming increasingly more unbearable. It was about 2′ 6″ away from my mind, not really connected to my body, but still intent on hurting me so terribly. (I can even feel the breath of it now as I am writing all this down.)

I had no appreciation of the rest of the operating site. By this time my mind was completely clear and I had no difficulty in thinking whatsoever.

I find this so distressing to recount that I will just concentrate on my sequence of thoughts.

"Oh no, this isn't supposed to happen, you're not supposed to feel the pain." To throw myself off the table? "No—the sterility. Oh, you can't move anyway." "Hang on it'll go in a minute" (c.f. the contractions). "What on earth is he doing?" I thought that if I could keep my mind on the progress of the operation, it would seem less distressing. "It's like the dentist." "It's still there, it's getting worse. Come on, hurry up, I can't hang on much longer." "It's like Dr X" (a consultant anaesthetist I used to work for, who did not believe intra-operative analgesia was necessary). "It's getting worse. Think about your breathing." I felt I had to distract myself, it was like a magnet, drawing my mind insistently back towards it. "Oh, you stupid fool, you're being ventilated." As my mind went to my chest, I realized it was gently moving up and down; for the first time I noticed the "bang" of the ventilator.

"That's no good." The only thing I could do was to hear—the only way I could help myself was to find something repetitive to listen to. As I searched around the room, I realized that the baby was screaming, loud and rhythmical screaming. "Listen to the baby, and the pain won't seem so bad." I fought with the pain and the sound for perhaps 20 seconds, but the pain was so bad, and worsening every second that my hearing was quite unable to hold it. Once my mind was fully back on the pain, I could hear nothing. In fact, it was getting very difficult for me to separate myself from the pain enough to think. The last thing I managed to think was: "What on earth have I said I'll let them do to me?"

I could not stand the pain for a split second longer. I tried to roll about (useless). From then onwards I absolutely and totally gave up (I almost made a decision to stop fighting—so laughably futile was the effort). The last memory I have is of trying to jerk my trunk off the left-hand side of the table.

I did not go unconscious; the pain did not stop. From then onwards there is a long period of amnesia until I woke up in bed in the ward.

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KETAMINE BLOCK OF BRONCHOSPASM IN EXPERIMENTAL CANINE ASTHMA

C. A. HIRSHMAN, H. DOWNES, A. FARBOOD AND N. A. BERGMAN

SUMMARY

Experimental asthma was induced in dogs previously sensitized to ascaris antigen by ventilation with ascaris antigen, in an aerosol, for 10 min. Before the administration of antigen, there was no significant difference in pulmonary airways resistance (R_L) during thiopentone and ketamine anaesthesia. In dogs anaesthetized with thiopentone, R_L increased significantly from a pre-antigen control of 0.36 ± 0.13 (mean ± SEM) kPa litre^{-1} s to 1.56 ± 0.38 at 5 min after administration of antigen. In dogs anaesthetized with ketamine, R_L before (0.30 ± 0.10) and 5 min after antigen (0.47 ± 0.18) was not significantly different. Beta adrenergic blockade with propranolol abolished the protective effect of ketamine so that there was no significant difference in the maximal increase (5 min after antigen) in R_L in dogs anaesthetized with ketamine (2.92 ± 0.74) or thiopentone (3.28 ± 1.16). Beta adrenergic blockade also increased pre-antigen R_L in both groups (ketamine 0.87 ± 0.24; thiopentone 0.77 ± 0.32).

The optimum technique for inducing general anaesthesia in the asthmatic patient with a full stomach is difficult to define. Since the threshold for initiation of bronchospasm by a variety of stimuli is lower in asthmatic patients, a rapid induction (to protect the airway against aspiration of gastric contents) may precipitate bronchospasm. Thus the effect of an i.v. anaesthetic on airway tone and responsiveness is an important consideration in the choice of anaesthesia. This study was designed to compare the effect of two anaesthetics, thiopentone and ketamine, in a dog model of allergic asthma.

METHODS

Ascaris suum worms were obtained from a slaughterhouse and purified according to the method of Mackler, Malley and Amkraut (1971). The purified preparation contained 3.46 mg of protein per millilitre. Fifteen studies were performed in Basenji Greyhound cross-bred dogs, each weighing about 20 kg. These animals were selected from a large dog colony because in addition to having a positive skin test to ascaris antigen, their airways were highly reactive to ascaris antigen in an aerosol.

Unpremedicated dogs were supported in a standing position by a sling. Anaesthesia was induced with either thiopentone 15 mg kg^{-1} i.v. or ketamine 10 mg kg^{-1} i.v., the trachea was intubated with a 9-mm tube following the administration of suxamethonium and the lungs were ventilated manually with 66% nitrous oxide in oxygen. Increments of either thiopentone or ketamine 60 mg were administered at 15-min intervals throughout the study. An oesophageal balloon (Dynasciences, Blue Bell, Pa.) was positioned under direct vision in the oesophagus to the position where recorded end-expiratory pressure was smallest. The balloon contained 0.8 ml of air. A separate catheter was placed in the oesophagus and suction was applied to remove air and liquids.

After compliance and resistance were measured, experimental asthma was induced according to the method of Gold and colleagues (1972). Ascaris protein 30 μg in 10 ml of water was delivered over 10 min by a nebulizer (Hudson 3000, Temecula, Calif.) inserted between the anaesthesia machine and the endotracheal tube. Pulmonary airways resistance (R_L) and compliance (C_L) were measured at 5-min intervals thereafter. During these measurements, ventilation was performed artificially for about 30 s with a piston-type ventilator (Harvard Apparatus Company, Millis, Mass.) from which the inspiratory and expiratory valves had been removed. The ventilator was set to deliver a tidal volume of 400 ml at a frequency of 15 b.p.m., and produced a regular sinusoidal flow pattern with a peak inspiratory flow

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equivalent to $2\pi f \times 0.2$ litre. Between measurements of R_L and C_L the lungs were ventilated manually.

Transpulmonary pressure was measured with a differential pressure transducer (290 Sanborn, Waltham, Mass.) connected to the oesophageal balloon and to a needle inserted into the tracheal tube. Airflow was measured with a Fleisch pneumotachograph head and a differential pressure transducer (267B Sanborn, Waltham, Mass.). Pressure and flow signals were recorded with a Sanborn 964 recorder (Waltham, Mass.).

Dynamic C_L was calculated by dividing tidal volume by the difference in pressure between points of zero flow. Before determining R_L, total transpulmonary pressure was measured at the point of maximum inspiratory flow. With the sinusoidal pattern used, this occurred exactly half-way through the inspiratory cycle and corresponded to an inspiratory volume of 200 ml greater than functional residual capacity. Pulmonary elastic pressure (P_{el}) at this point was calculated by dividing 200 ml by compliance. Pressure required to overcome flow resistance (P_{res}) was calculated by subtracting elastic pressure from total transpulmonary pressure. R_L was calculated by dividing P_{res} by instantaneous flow rate ($\dot{V}$) at this point:

$$R_L = P_{res}/\dot{V}$$

All volumes were corrected to BTPS. R_L and C_L were calculated from a mean of seven consecutive breaths.

E.c.g. was recorded continuously using a Grass Model 79 Recorder (Quincy, Mass.). End-tidal carbon dioxide concentration was monitored continuously using a Beckman LB 1 infra-red carbon dioxide analyser (Palo Alto, Calif.).

To evaluate the possible role of the sympathetic nervous system antigen-induced changes in R_L and C_L were tested after beta adrenergic block with propranolol 2 mg kg^{-1}. The propranolol was administered by slow i.v. injection over a 10-min interval which was completed 5 min before induction of anaesthesia. The extent of beta adrenergic blockade was determined on a separate day using a standard isoprenaline challenge, according to the method of Cleaveland, Rangno and Shand (1972). Isoprenaline dose ratios (fig. 1) after propranolol 2 mg kg^{-1} i.v. varied from 84 to 394.

R_L and C_L were compared during thiopentone and ketamine anaesthesia, with and without beta blockade, pre-antigen and at each 5-min interval by a two-way analysis of variance (Scheffé, 1959) and Student–Newman Kuls test for multiple comparison (Steele and Torrie, 1960). The level of statistical significance was 0.05.

RESULTS

Before exposure to antigen, R_L was not significantly different during ketamine and thiopentone anaesthesia (table I). During thiopentone anaesthesia, 5 min after completion of the administration of antigen R_L increased significantly to 1.56 ± 0.38 kPa litre^{-1} s,

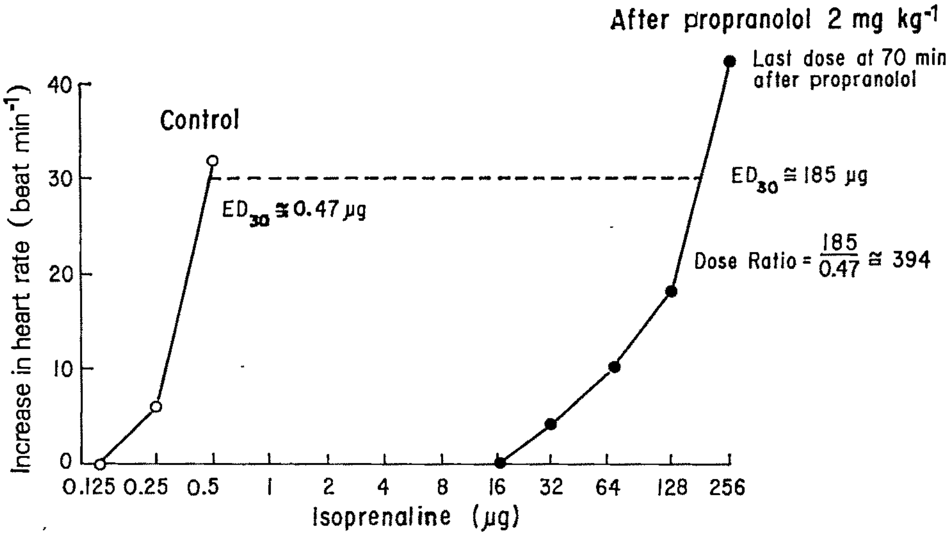

FIG. 1. Effects of propranolol 2 mg kg^{-1} i.v. on the isoprenaline test in one dog. In this case, the dose ratio was 394.

TABLE I. *Pulmonary airways resistance* (R_L) (*kPa litre*$^{-1}$ *s*) *before and 5 min after administration of ascaris antigen*

	Before	After	*P*
Ketamine	0.30±0.10	0.47±0.18	n.s.
Ketamine + propranolol	0.87±0.24	2.92±0.74	<0.05
Thiopentone	0.36±0.13	1.56±0.38	<0.05
Thiopentone + propranolol	0.77±0.32	3.28±1.16	<0.05

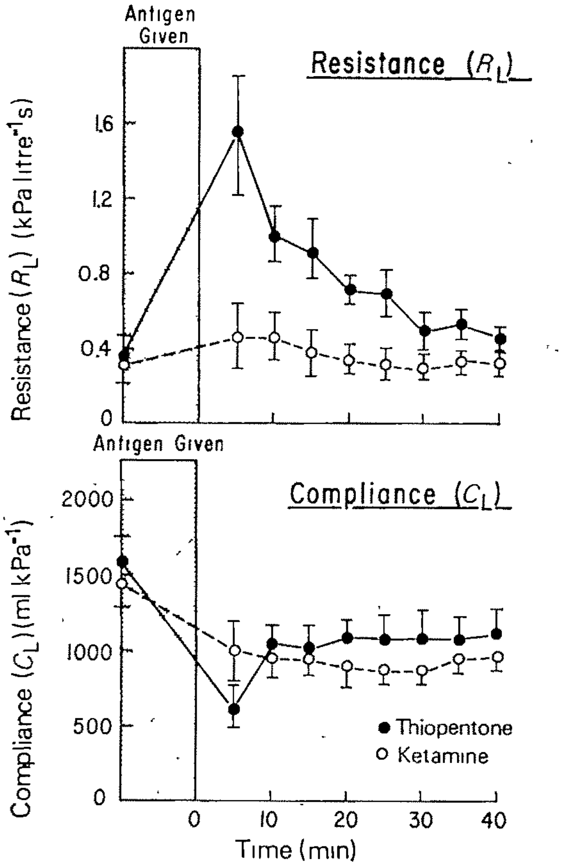

FIG. 2. Changes in pulmonary airways resistance and compliance following 10 min of ascaris antigen during ketamine and thiopentone anaesthesia.

gradually decreasing to 0.82±0.14 and 0.58±0.10 at 15 and 30 min respectively (fig. 2). In animals anaesthetized with ketamine, administration of antigen did not produce a significant increase in R_L (fig. 2). Five minutes after completing administration, R_L was 0.47±0.18 kPa litre^{-1} s and was 0.36±0.10 and 0.34±0.12 at 15 and 30 min respectively.

After beta adrenergic blockade, but before administration of antigen, R_L was significantly greater with both anaesthetics (table I). After propranolol, antigen administration increased R_L significantly in dogs receiving either thiopentone or ketamine (table I) and there was no significant difference between the two anaesthetics. C_L decreased significantly after administration of antigen during ketamine and thiopentone anaesthesia both before and after beta adrenergic blockade (figs 2 and 3).

The mean end-tidal carbon dioxide concentration was 5% in all studies and there was no significant difference between dogs anaesthetized with thiopentone or ketamine.

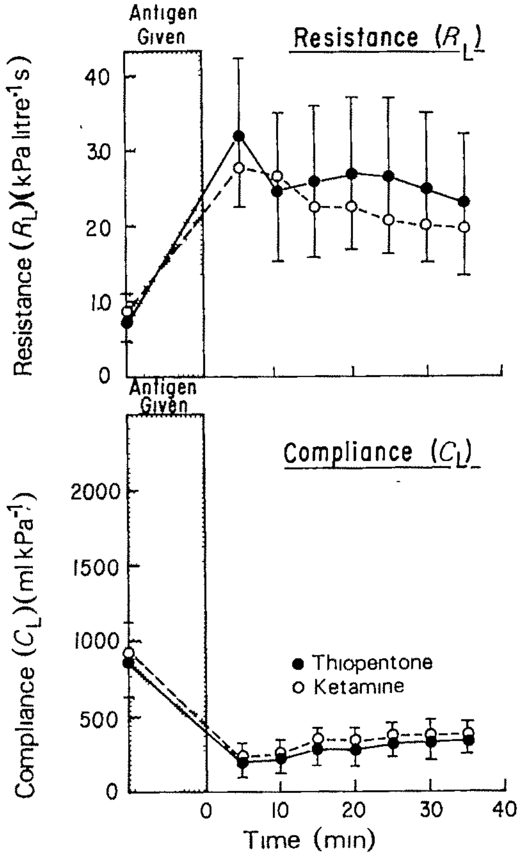

FIG. 3. Changes in pulmonary airways resistance and compliance following 10 min of ascaris antigen during ketamine and thiopentone anaesthesia after beta adrenergic blockade.

DISCUSSION

Betts and Parkin (1971) and Corssen and others (1972) reported that ketamine was a safe anaesthetic in patients with asthma but they did not measure airways resistance. Huber and others (1972) measured airway resistance in asthmatic patients and found a decrease in some patients in response to ketamine, but the drug was given after the patients were anaesthetized with halothane and nitrous oxide. It is not clear if this response was produced by ketamine or by halothane. On the other hand, Waltemath and Bergman (1974) showed that ketamine did not decrease airways resistance (R_L) in non-asthmatic patients in whom R_L was increased artificially with water in an aerosol.

Our study differs from previous studies in which attempts were made to reverse rather than prevent bronchospasm, and which used ketamine in patients already anaesthetized with other drugs. Other anaesthetic drugs may modify considerably any changes produced by ketamine via autonomic pathways.

Hypersensitivity to ascaris antigen occurs in dogs as a result of a parasitic infection and the physiological and radiological changes elicited by antigen in an aerosol are similar to those observed in humans with asthma (Patterson, Roberts and Pruzansky, 1965; Gold et al., 1972). The marked increase in airways resistance is reversed rapidly by bronchodilators (Gold et al., 1972). Tantalum bronchograms show that increased R_L is a result of constriction of both large and small airways (Kessler et al., 1973). Gold and others (1977) have shown recently that asthma induced by ascaris antigen results in degranulation of mast cells with release of histamine in addition to vagally mediated reflex bronchospasm (Gold, Kessler and Yu, 1972).

Our study shows clearly that ketamine was superior to thiopentone in preventing antigen-induced bronchospasm in a dog model of asthma.

Since R_L varies inversely with lung volume (Fenn and Rahn, 1964), ventilation was controlled and all measurements of R_L were made at the same lung volume above functional residual capacity. It is possible that total lung volume differed slightly with the two anaesthetics and with beta adrenergic blockade, but it is unlikely that small changes in lung volume could account for the large differences in R_L measured. Changes in end-tidal carbon dioxide concentration are known to alter R_L (Ingram, 1975) but end-tidal carbon dioxide concentrations were monitored constantly and were similar during ketamine and thiopentone anaesthesia.

Ketamine may protect against ascaris-induced bronchospasm by several different mechanisms. Lundy, Gowdey and Calhoun (1974) found, in guineapig tracheal muscle *in vitro*, that ketamine in concentrations slightly greater than those found in plasma during ketamine anaesthesia exerted a direct dose-dependent relaxant effect. They found also that smaller concentrations of ketamine, similar to plasma concentrations during anaesthesia, were effective in relaxing carbachol-induced contractions. Wanna and Gergis (1978) found that larger concentrations produced a slight relaxation of histamine-induced contractions.

McGrath, MacKenzie and Miller (1975) found that *in vivo* ketamine blocked bradycardia produced by stimulation of the depressor nerve, and attributed this to a central depressant action since bradycardia could still be produced by stimulation of vagal efferents.

In our studies, vagal block, either central or peripheral, and direct relaxant effects on smooth muscle could have contributed to the protective effect of ketamine against antigen-induced asthma. However, the major component was clearly sympathomimetic. After beta adrenergic blockade, ascaris antigen produced virtually an identical increase in R_L in dogs receiving ketamine or thiopentone. The sympathomimetic effects of ketamine are well recognized and have been attributed to baroreceptor desensitization (Dowdy and Kaya, 1968), central sympathetic stimulation (Wong and Jenkins, 1974) and potentiation of endogenously released catecholamines secondary to block of re-uptake (Montel et al., 1973; Nedergaard, 1973). Our studies do not permit us to discriminate between these mechanisms.

Beta adrenergic blockade significantly increased R_L and decreased C_L before administration of antigen after both thiopentone and ketamine. This indicates the presence of resting beta adrenergic bronchodilator activity. This is in agreement with studies by MacDonald, Ingram and McNeill (1967) and Richardson and Sterling (1969), who showed marked increases in airway resistance after beta blockade in asthmatic subjects.

C_L decreased following exposure to antigen during both ketamine and thiopentone anaesthesia. Beta adrenergic blockade exaggerated C_L change, which again was similar following thiopentone and ketamine. These changes in C_L may represent tissue oedema and airway secretions that are not readily reversed by the sympathetic nervous system (Bouhuys and Van de Woestijne, 1971).

Although we cannot exclude effects of ketamine on vagal tone or directly on smooth muscle, the protective effect of ketamine was abolished by beta adrenergic blockade. Therefore, the sympathomimetic effects of ketamine appear to be mainly responsible for its protective action in allergen-induced bronchospasm, possibly by inhibition of mediator release from mast cells (Kaliner, Orange and Austen, 1972) in addition to relaxation of airway smooth muscle.

Ketamine may be the agent of choice for induction of anaesthesia in asthmatic patients, especially those in whom a rapid induction of anaesthesia is required.

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BLOCAGE PAR LA KETAMINE DES BRONCHOSPASMES D'UN ASTHME EXPERIMENTAL CHEZ LES CHIENS

RESUME

Un asthme expérimental a été provoqué sur des chiens que l'on avait précédemment sensibilisés aux antigènes d'ascaris en les ventilant avec des antigènes d'ascaris en aérosol pendant 10 mn. Avant l'administration d'antigènes, il n'y avait pas eu de différence sensible dans la résistance des passages d'air pulmonaires (R_L) pendant l'anesthésie au thiopentone ou à la kétamine. Sur les chiens anesthésiés au thiopentone, la R_L a augmenté d'une manière significative d'une valeur témoin pré-antigènes de 0,36 ± 0,13 (moyenne ± écart type) kPa litre^{-1} s, à 1,56 ± 0,38 cinq minutes après l'administration d'antigènes. Sur les chiens anesthésiés à la kétamine, la R_L n'a pas été très différente avant (0,30 ± 0,10) et 5 mn après (0,47 ± 0,18) l'administration d'antigènes. Le blocage adrénergique béta à l'aide de propranolol a aboli l'effet protecteur de la kétamine de telle sorte qu'il n'y a pas eu de différences importante dans l'augmentation maximale (5 mn après l'administration d'antigènes) de la R_L chez les chiens anesthésiés à l'aide de kétamine (2,92 ± 0,74) ou de thiopentone (3,28 ± 1,16). Le blocage adrénergique béta a aussi augmenté la R_L pré-antigènes dans les deux groupes (kétamine 0,87 ± 0,24; thiopentone 0,77 ± 0,32).

BLOCKIERUNG VON BRONCHIALKRAMPF IN EXPERIMENTELLEM ASTHMA IN HUNDEN DURCH KETAMIN

ZUSAMMENFASSUNG

In vorher auf Spulwurm sensibilisierten Hunden wurde durch 10 Min lange Ventilierung mit Spulwurmantigen in einem Aerosol experimentelles Asthma herbeigeführt. Vor der Antigenverabreichung bestand kein bedeutsamer Unterschied im Widerstand der Lungenluftwege (R_L) während der Thiopenton- und Ketaminnarkose. Bei mit Thiopenton narkotisierten Hunden stieg R_L bedeutsam von einem Kontrollpegel von 0,36 ± 0,13 (Mittel + SEM) kPa litre^{-1} s^{-1} vor Verabreichung des Antigens 5 Min nach Verabreichung des Antigens auf 1,56 ± 0,38 an. Bei mit Ketamin narkotisierten Hunden bestand kein bedeutsamer Unterschied in R_L vor (0,30 ± 0,10) und 5 Min nach (0,47 ± 0,18) Verabreichung des Antigens. Beta-adrenergische Blockierung mit Propanolol hob die Schutzwirkung von Ketamin auf, so dass bei mit Ketamin (2,92 ± 0,74) bzw. Thiopenton (3,28 ± 1,16) narkotisierten Hunden kein bedeutsamer Unterschied in dem Hochstanstieg (5 Min nach Antigenverabreichung) in R_L bestand. Die beta-adrenergische Blockierung erhöhte auch bei beiden Gruppen (Ketamin 0,87 ± 0,24; Thiopenton 0,77 ± 0,32) den vor der Antigenverabreichung bestehenden R_L.

BLOQUEO POR QUETAMINA DEL BRONCOESPASMO EN ASMA CANINO EXPERIMENTAL

SUMARIO

Se indujo asma experimental en perros previamente sensibilizados al antígeno del ascaris por ventilación de antígeno de ascaris mediante aerosol de una duración de 10 min. Antes de la administración del antígeno, no había diferencia significativa en la resistencia de las vías respiratorias (RVR) durante la anestesia por quetamina y tiopentona. En los perros anestesiados con tiopentona, la RVR aumentó significativamente de un control pre-antígeno de 0.36 ± 0.13 (promedio ± SEM) kPa litro^{-1} s hasta 1.56 ± 0.38, cinco minutos después de la administración del antígeno. En perros anestesiados con quetamina, no difería sensiblemente la RVR inicial (0.30 ± 0.10) de la cinco minutos después del antígeno (0.47 ± 0.18). El bloqueo adrenérgico beta con propranolol abolía el efecto de protección de la quetamina de manera que no hubo diferencia significativa en el aumento máximo (5 min. después del antígeno) en la RVR de perros anestesiados con quetamina (2.92 ± 0.74) o con tiopentona (3.28 ± 1.16). El bloqueo adrenérgico beta también ocasionó un aumento de la RVR pre-antígena en ambos grupos (quetamina 0.87 ± 0.24; tiopentona 0.77 ± 0.32).

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PROLONGATION BY BILE SALTS OF THE DURATION OF ACTION OF A STEROIDAL NEUROMUSCULAR BLOCKING AGENT

R. J. VONK, P. WESTRA, M. C. HOUWERTJES AND S. AGOSTON

SUMMARY

The influence of bile salts on the duration of action of the steroidal non-depolarizing neuromuscular blocking agent ORG 6368 was investigated in cats. The intravenous administration of ORG 6368 (100 μg/kg body wt) caused a maximum neuromuscular blockade of 71 ± 6% with a duration of action of 3.4 ± 0.1 min. However, intraportal administration of the same dose caused no significant neuromuscular blockade. Following an infusion of dehydrocholate 320 μmol, lasting for 8 min, the magnitude and the duration of action of the neuromuscular blockade produced by ORG 6368 were increased markedly. This effect of the bile salt is possibly a result of inhibition of the hepatic uptake of ORG 6368, thereby retarding its disappearance from the plasma and consequently prolonging the neuromuscular blockade. The neuromuscular blocking effect of intraportally administered gallamine (1 mg/kg body wt) was not influenced significantly by the infusion of dehydrocholate.

The durations of action of neuromuscular blocking agents are determined by a number of factors including drug–receptor interactions, possible cholinesterase inhibition by the relaxant drug (Foldes, 1971, 1975—personal communications; Schuh, 1977) and their pharmacokinetic behaviour. In particular, renal and hepatic clearance (Marsh, 1952; Kalow, 1953; Cohen, Corbascio and Fleischli, 1965; Agoston, Kersten and Meijer, 1973; Agoston et al., 1973) and binding to "acceptor tissue depots" (Chagas, 1962; Cohen, Hood and Golling, 1968; Asghar and Roth, 1971; Shindo et al., 1974) are important pharmacokinetic factors in determining the magnitude and duration of the neuromuscular blockade. Pharmacokinetic studies of various non-depolarizing muscle relaxants indicated that gallamine (Mushin et al., 1949; Agoston et al., 1978) and alcuronium (Raaflaub and Frey, 1972) are excreted mainly by the kidneys. The liver appears to play a role in the disappearance, from the plasma, of tubocurarine (Cohen, Brewer and Smith, 1967; Meijer and Scaf, 1968), pancuronium (Agoston et al., 1973; Buzello, 1975) and hexafluorenium (Meijer, Vermeer and Kwant, 1971). In the cat, hepatic uptake is an important factor in the plasma disappearance of a number of steroidal neuromuscular blocking agents, such as pancuronium, dacuronium and ORG 6368 (2β,16β-dipiperidino-5α-androstan-3α-ol acetate dimethobromide) (Agoston, Kersten and Meijer, 1973; Agoston et al., 1977). Therefore, alterations in hepatic function may influence the pharmacokinetics, and consequently the duration of action, of these drugs. It was reported that, in patients with cholestasis, the duration of action of pancuronium was prolonged (Somogyi, Shanks and Triggs, 1977). Recently, Vonk and others (1978a, b) observed that bile salts inhibited the hepatocellular transport of the organic cations tubocurarine and acetylprocainamide ethobromide in intact rats, isolated perfused rat livers and isolated hepatocytes.

The aim of this study was to investigate the possible role of bile salts in the hepatic transport of neuromuscular blocking agents, which could lead to an increase in the duration of action of these compounds. The experiments were performed with ORG 6368 and gallamine triethiodide. ORG 6368 is a short-acting analogue of pancuronium bromide (Sugrue and Duff, 1973). It has been shown (Agoston et al., 1977) that its duration of action is determined mainly by hepatic clearance. In contrast, the plasma disappearance of gallamine triethiodide, which is determined by renal function, theoretically should not be changed by alterations in the hepatic transport systems of drugs.

METHODS

Animal experiments

All experiments were carried out on adult cats (2–4 kg body wt) of either sex under pentobarbitone anaesthesia. After orotracheal intubation with a

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cuffed tube, mechanical ventilation with air was maintained at a rate of 30 b.p.m. with a tidal volume of 34 ml. In order to check the general condition of the cat, e.c.g. and mean arterial pressure were monitored. Mean arterial pressure was not less than 100 mg Hg in all experiments. Body temperature was kept constant at 37–38 °C by heating the operating table. To replace fluid loss, glucose 2.5% and saline 0.45% were infused through a polythene cannula via an external jugular vein. Neuromuscular studies (isometric twitch tension) were performed on the tibialis anterior muscle which was stimulated through its motor nerve with supramaximal square wave pulses of 0.2 ms duration at a frequency of 0.1 Hz. Following the administration of heparin 2500 i.u., a silicon catheter was placed in the hepatic portal vein to permit the administration of drugs into the portal system. After the administration of the neuromuscular blocking drugs, arterial blood samples were taken at the time when twitch tension approached 50% of control. Bolus injections of the neuromuscular blocking agents were made within periods of 5 s. The bile salts, dehydrocholate (Fluka A. G.) and chenodeoxycholate (Falk GmbH & Co), were administered by continuous infusions through the catheter placed in the portal vein. In order to avoid accumulation, ORG 6368 (Organon Ltd) was administered at intervals of at least 30 min. Gallamine triethiodide (Flaxedil, Specia) was injected at intervals of 60 min.

Chemical analysis

ORG 6368 in plasma was estimated according to the procedures described before (Kersten, Meijer and Agoston, 1973; Agoston et al., 1977).

Statistical analysis

Statistical comparisons were made using Student's *t* test with a 95% significance level. The values given are mean values ± SEM.

RESULTS

The i.v. administration of ORG 6368 100 μg/kg body wt produced a maximal depression of the control twitch height to 71 ± 6% ($n = 6$) (fig. 1A; table I). The time to 90% recovery of control twitch tension was 3.4 ± 0.1 min. When the same dose of ORG 6368 was administered through the catheter in the portal vein, a neuromuscular blockade of only 2 ± 2% was

TABLE I. *Neuromuscular blockade, duration of action to 90% recovery of control twitch tension following i.v. and intraportal administration of ORG 6368 100 μg/kg body wt in cats (n = 6). — = not measured; 0 = not measurable*

Administration	Maximal neuromuscular blockade (%)	Duration of action (min)	ORG 6368 concn at 50% recovery (μmol)
I.v.	71 ± 6	3.4 ± 0.1	0.15 ± 0.02
Intraportal	2 ± 2	0	0
Intraportal (+ dehydrocholate)	70 ± 12	5.5 ± 0.6	0.29 ± 0.06
Intraportal	7 ± 3	0	0
I.v.	71 ± 6	4.0 ± 0.1	—

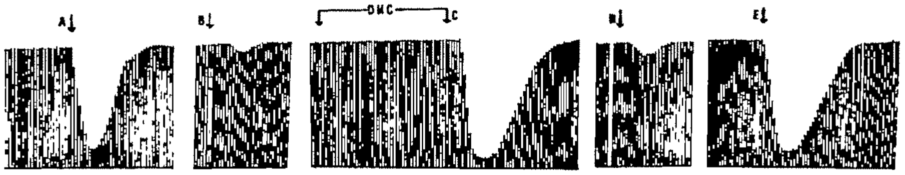

FIG. 1. Influence of dehydrocholate on the pattern of action of ORG 6368, a steroidal non-depolarizing neuromuscular blocking agent. A: i.v. injection of ORG 6368; B: intraportal injection of ORG 6368; C: intraportal injection of ORG 6368 immediately after intraportal infusion of dehydrocholate 320 μmol in 8 min; note the lack of any change in the twitch height during the bile salt infusion; D: intraportal injection of ORG 6368 about 2 h after dehydrocholate infusion; E: i.v. injection of ORG 6368.

produced (fig. 1B). The influence of bile salts was subsequently investigated. Dehydrocholate was infused at a rate of 40 μmol min^{-1} over 8 min. The intraportal injection of ORG 6368 100 μg/kg body wt immediately after the infusion of the bile salt resulted in 70 ± 12% depression of twitch height and a duration to 90% recovery of 5.6 ± 0.6 min (fig. 1C). This potentiating effect of dehydrocholate was reversible and lasted from 30 min to approximately 180 min.

When an intraportal injection of ORG 6368 100 μg/kg body wt was given, a neuromuscular blockade of 7 ± 3% (fig. 1D) was subsequently produced, a pattern which was comparable to that before the administration of the bile salt. The i.v. administration of ORG 6368 caused approximately the same neuromuscular blockade as before the dehydrocholate administration (table I: 71 ± 6%, lasting 4.0 ± 1 min).

In contrast to the observations obtained with ORG 6368, the neuromuscular blocking effect of intraportally administered gallamine 1 mg/kg body wt was not influenced significantly by dehydrocholate infusion. Gallamine administered in this dose caused a 71 ± 8% depression of twitch height with a duration to 90% recovery of 8.4 ± 1.0 min; after dehydrocholate infusion these values were 74 ± 5% and 9.5 ± 1.3 min respectively ($n = 4$).

The influence of dehydrocholate on the relationship between plasma concentration of ORG 6368 and the neuromuscular blocking effect is shown in table I. At 50% recovery of the twitch tension, the concentration of ORG 6368 was significantly higher in the presence of dehydrocholate.

DISCUSSION

The marked decrease in the effectiveness of ORG 6368 when injected into the portal vein, rather than into the general circulation, is explained by the high hepatic clearance of this drug (Agoston et al., 1977). Differences in the patterns of efficacy of neuromuscular blocking agents injected by different routes have also been described by Hughes (1972). In contrast to that of ORG 6368, gallamine's efficacy was not reduced when it was injected intraportally—an observation compatible with the absence of any important role of the liver in the plasma clearance of gallamine (Feldman, Cohen and Galling, 1969; Agoston et al., 1978). During the infusion in the present study, and in separate *in vitro* experiments (unpublished data) in the rat phrenic nerve–diaphragm preparation, dehydrocholate (concentration up to 2.0 mmol) and chenodeoxycholate (concentration up to 0.2 mmol) did not influence the indirectly evoked twitch contractions.

The effects of the semi-synthetic bile salt dehydrocholate were studied in these experiments because this substance has previously been found to modify the hepatic transport of drugs (Vonk et al., 1978a, b) and, in the doses used, it is free from complicating cardiovascular actions. Its effects on the actions of neuromuscular blocking drugs were compared with, and found to be qualitatively similar to, those of the naturally occurring bile salt chenodeoxycholate.

Either bile salt, when infused into the portal vein, potentiated the neuromuscular blocking action of ORG 6368 injected by the same route. That the potentiating action was not the result of a peripheral sensitizing action of the bile salts at the neuromuscular junction was shown by the observation that gallamine was not similarly potentiated. Furthermore, the increased efficacy of intraportally injected ORG 6368 in the presence of bile salts was associated with an increased plasma concentration of the drug. Thus, it seems clear that the potentiating action of bile salts on ORG 6368 takes place in the liver, and occurs because the bile salts impair the net hepatic uptake of the neuromuscular blocking drug. The mechanism underlying this effect is not fully established. Inhibition of biliary excretion is unlikely, because biliary excretion of ORG 6368 in the cat is a relatively unimportant route of elimination (12% of the dose in 8 h; Agoston et al., 1977).

The bile salts do not appear to displace ORG 6368 from the liver since, in unpublished experiments, we have shown that after previous loading of the liver with ORG 6368, infusions of bile salts do not produce neuromuscular block. Therefore, we conclude that the bile salts act by inhibiting the primary hepatic uptake process of ORG 6368, a conclusion which is in agreement with earlier studies in which the interactions of bile salts with tubocurarine or acetylprocainamide ethobromide were studied (Vonk et al., 1978a, b). The results suggest that in patients with an increased plasma concentration of bile salts, neuromuscular blocking agents that are cleared from the plasma by the liver may have an unusually prolonged duration of action.

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PROLONGATION DE LA DUREE DE L'ACTION D'UN AGENT DE BLOCAGE NEUROMUSCULAIRE STEROIDE PAR LES SELS BILIAIRES

RESUME

On a fait des recherches sur des chats pour étudier l'influence des sels biliaires sur la durée de l'action de l'agent de blocage neuromusculaire stéroïde non dépolarisant ORG 6368. L'administration intraveineuse d'ORG 6368 (à raison de 100 µg/kg de poids du corps) a provoqué un blocage neuromusculaire maximum de 71 ± 6% avec une durée d'action de 3,4 ± 0,1 mn. Cependant, l'administration intraportale de la même dose n'a provoqué aucun blocage neuromusculaire significatif. Après l'infusion de 320 µmol de déhydrocholate, d'une durée de 8 mn, l'importance et la durée d'action du blocage musculaire produit par l'ORG 6368 ont été distinctement et fortement accrues. Ces effets des sels biliaires sont probablement le résultat de l'inhibition de la fixation hépatique de l'ORG 6368, ce qui en a retardé la disparition du plasma et a par conséquent prolongé le blocage neuromusculaire. L'effet de blocage neuromusculaire de la gallamine administrée par voie intraportale (à raison de 1 mg/kg de poids du corps) n'a pas été influencé d'une manière significative par l'infusion de déhydrocholate.

VERLÄNGERUNG DER WIRKUNGSDAUER EINES AUF STEROIDEN AUFGEBAUTEN NEUROMUSKULÄREN BLOCKIERUNGSMITTELS DURCH GALLENSALZE

ZUSAMMENFASSUNG

Es wurde der Einfluss von Gallensalz auf die Wirkungsdauer des auf Steroiden aufgebauten, nicht depolarisierenden neuromuskularen Blockierungsmittels ORG 6368 bei Katzen untersucht. Die intravenöse Verabreichung von ORG 6368 (100 µg/kg Korpergewicht) bewirkte eine maximale neuromuskuläre Blockierung von 71 ± 6% mit

einer Wirkungsdauer von 3,4 ± 0,1 Min. Eine Eingabe derselben Dosis in die Pfortader verursachte jedoch keine bedeutsame neuromuskuläre Blockierung. Nach einer 8 Min dauernden Infusion von 320 μmol Dehydrocholat war die Stärke und Wirkungsdauer der durch ORG 6368 hervorgerufenen neuromuskulären Blockierung bedeutend erhoht. Diese Wirkung des Gallensalzes ergibt sich möglicherweise aus einer Hemmung der hepatischen Aufnahme von ORG 6368, wodurch sein Verschwinden aus dem Blutplasma verzögert und die neuromuskuläre Blockierung dementsprechend verlängert wird. Die neuromuskuläre Blockierungswirkung von in die Pfortader eingegebenem Gallamin (1 mg/kg Körpergewicht) wurde durch die Infusion von Dehydrocholat nicht wesentlich beeinflusst.

PROLONGACION DE LA DURACION DE ACCION DE UN AGENTE DE BLOQUEO NEUROMUSCULAR ESTEROIDAL POR SALES BILIARES

SUMARIO

Se investigó en gatos la influencia de la sal biliar sobre las duraciones de acción del agente bloqueador neuromuscular no-depolarizante esteroidal ORG 6368. La administración intravencsa de ORG 6368 (100 μg/kg de peso corporal) causó un bloqueo neuromuscular máximo de 71 ± 6%, con una duración de acción de 3.4 ± 0.1 min. Sin embargo, la administración intraportal de la misma dosis no causó bloqueo neuromuscular significativo. Después de una infusión de 320 μmol de dehidrocolato, de 8 min de duración, aumentaron notable y significantemente la magnitud y la duración de acción del bloqueo neuromuscular producido por el ORG 6368. Posiblemente, este efecto de la sal biliar resulte de la inhibición de la captación hepática de ORG 6368, demorando por causa de ello su disparición de la plasma y prolongando por ende el bloqueo neuromuscular. La infusión de dehidrocolato no influenció de manera significativa el efecto bloqueador neuromuscular de la galamina administrada por vía intraportal (1 mg/kg de peso corporal).

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EFFECT OF ACUTE HYPOCAPNIA ON SOME ASPECTS OF RENAL FUNCTION IN ANAESTHETIZED DOGS

J. M. HUNTER, R. S. JONES, G. LAMPLUGH AND J. E. UTTING

SUMMARY

Hypocapnia was induced in dogs lightly anaesthetized with nitrous oxide and fentanyl. Measurements were made of estimated renal plasma flow (ERPF), glomerular filtration rate, vascular resistance and urine production. During the (short) duration of the experiments hypocapnia was found to be associated with ERPF twice that during normocapnia. Glomerular filtration rate and urine output were increased by hypocapnia in an approximately similar proportion, whilst renal vascular resistance halved. Though some of the experimental animals had a degree of metabolic acidosis this was thought not to have greatly influenced the results.

The most important physiological components of the renal vasculature, the afferent and efferent glomerular arterioles and vasa recta, have a muscular component in their walls with sympathetic, and probably also parasympathetic, innervation. Nearly all the renal blood flow passes through these vessels and their calibre, therefore, is a major determinant of renal blood flow (RBF). Moreover, the calibre of the afferent and the efferent arterioles, both in absolute terms and relative to one another, is an important determinant of the glomerular filtration rate (GFR).

In general terms, carbon dioxide has a direct effect on blood vessels, producing vasodilatation, and an indirect effect, mediated by the sympathetic nervous system, causing vaso-constriction. It would be expected, therefore, that changes in carbon dioxide tension would have a considerable effect on renal function. It is also clearly not possible to predict the effect of hypocapnia on such variables as RBF and GFR without experimental investigation.

Acute changes in $P\text{CO}_2$ are common in anaesthetic practice and a survey of the literature revealed no adequate indication of the effect of hypocapnia on renal function. In an attempt to answer this question a series of experiments was conducted on dogs. An acute change in $P\text{CO}_2$ was imposed on lightly anaesthetized animals during controlled ventilation of the lungs, whilst at the same time renal blood flow, glomerular filtration rate and renal vascular resistance were measured. The duration of each period of hypocapnia and normocapnia was 90 min.

METHODS

Fourteen experiments were conducted on five healthy mature Labrador dogs, weighing 14–25 kg. In half of the experiments $P\text{CO}_2$ was maintained initially at a normal value and hypocapnia induced later, whilst in the other half the order was reversed. RBF and GFR were determined throughout the course of the experiment.

Preparation before operation

The dogs were fed a normal, commercial diet, but were starved overnight and water was withheld on the days of the experiments. Exteriorization of the carotid artery was performed at least 3 weeks before the initial experiments to provide access for repeated arterial cannulation.

At least 3 weeks before each experiment, blood (500 ml) was removed and stored in acid–citrate–dextrose solution. This was used as an autotransfusion to replace blood lost by sampling.

Anaesthesia

No premedication was given. Anaesthesia was induced with thiopentone 250 mg i.v. and fentanyl 200 μg, preceded by atropine 0.6 mg; alcuronium 2.5 mg was administered to provide neuromuscular blockade. Following tracheal intubation, anaesthesia was maintained with a mixture of fentanyl at the rate of 0.4 μg min^{-1}. Incremental doses of alcuronium 1.25–2.5 mg were given when indicated.

Intermittent positive pressure ventilation was effected with a Beaver ventilator (Mark II) attached

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to the expiratory limb of a Mapleson E type circuit via a Ruben non-return valve. The frequency of ventilation was 20 cycles min^{-1} and the tidal volume approximately 40 ml kg^{-1} body weight. End-expiratory carbon dioxide tension ($P\text{E}'_{\text{CO}_2}$) could be changed from normocapnia to hypocapnia or *vice versa* by increasing or decreasing the fresh gas flow supplied to the circuit, without changing appreciably the intra-thoracic pressure.

$P\text{E}'_{\text{CO}_2}$ was monitored throughout the experiment using a Beckman (LB2) infra-red analyser which had been calibrated previously with two appropriate gas mixtures the composition of which had been determined with a Haldane apparatus: this measurement was used merely as an approximate and rapid guide to Pa_{CO_2}.

Throughout anaesthesia the dog lay on a warming blanket and was covered to minimize changes in body temperature: rectal temperature was monitored throughout.

Residual effects of alcuronium were antagonized at the end of anaesthesia with neostigmine 5 mg (given with atropine 1.2 mg). Following the return of spontaneous ventilation the endotracheal tube was removed and the animal was allowed to recover in a quiet environment.

Further experimental preparation

After induction of anaesthesia a cannula was inserted into the carotid loop to monitor arterial pressure and to facilitate blood sampling. A second cannula was introduced to the inferior vena cava for the preliminary infusion of hypotonic saline and for administering para-aminohippuric acid (PAH), inulin and fentanyl (see below). A third cannula was inserted into a peripheral vein for autotransfusion of previously stored blood in quantities equal to that of the blood lost during sampling.

The bladder was catheterized, emptied, and subsequently allowed to drain freely into a measuring cylinder; urinary volume was measured after manual expression of the bladder. To produce an adequate flow of urine for the determination of RBF and GFR (that is at least 0.5 ml min^{-1}) hypotonic saline (0.45%) 100 ml was administered over the hour following induction of anaesthesia.

The animal was considered to have attained a steady physiological state about 1 h after induction of anaesthesia: at this point the loading doses of PAH and inulin were commenced.

Monitoring

Arterial and venous pressures were measured using suitable transducers (Bell and Howell type 4/327/L221) and displayed on a Devices recorder (MX2R): the transducers were calibrated against columns of mercury and water respectively in the usual way.

Mean arterial pressure was taken as the sum of the diastolic pressure and one-third of the pulse pressure. This was considered to be equal to the pressure in the renal artery when determinations of renal vascular resistance were made. The mean pressure in the IVC was estimated from the pressure trace: this was assumed to be equal to the pressure in the renal vein.

Determination of RBF and GFR

The methods used were similar to those described by Smith (1956). The loading doses of PAH (10 mg kg^{-1}) and of inulin (60 mg kg^{-1}) were given over a 10-min period 1 h or more after anaesthesia had been induced: immediately before starting this infusion a sample of blood was withdrawn to provide "blank" values for calibration purposes. Thereafter, plasma concentrations of both substances were maintained as constant as possible using an infusion of 2 ml min^{-1} of a solution containing PAH (2.5 mg ml^{-1}) and inulin (5 mg ml^{-1}) in hypotonic saline (0.45%); to this infusion was added fentanyl 0.2 μg ml^{-1}. A constant infusion pump was used for this purpose (Watson-Marlow, Mark 3).

Arterial blood samples (12 ml) were withdrawn for the estimation of PAH, inulin, haematocrit (Hct) and blood-gas estimation at intervals of 30 min during the experiment; there were thus three samples taken during the periods of normocapnia and three during hypocapnia.

Before blood samples were taken urine was collected for a period of 5 min; the rate of formation was noted and the sample was subsequently analysed for PAH and inulin concentration.

Estimated renal plasma flow (ERPF) was measured (ml min^{-1}) according to the clearance equation:

$$C_{\text{PAH}} = \text{ERPF} = \frac{U_{\text{PAH}}}{P_{\text{PAH}}} \times V$$

where C_{PAH} is the renal clearance of PAH, U_{PAH} and P_{PAH} are, respectively, the concentrations of PAH in urine and plasma and V is the volume of urine produced per minute.

The equation $$\text{RBF} = \text{ERPF} \times \frac{100}{100-\text{Hct}}$$

gives a correct value for RBF only if the extraction of PAH (E_{PAH}) is 100%. The actual extraction was tested during hypocapnia on three occasions by placing a catheter in the renal vein and withdrawing samples from it. Subsequently the experimental animal was sacrificed.

Renal vascular resistance (RVR) was derived from:

$$RVR = \frac{\text{mean arterial pressure} - \text{mean pressure IVC}}{RBF}$$

This was expressed per 100 g kidney weight, the weight of the kidney being taken as 0.03% of total body weight.

GFR was determined in a similar way using the inulin clearance equation:

$$GFR = C_{IN} = \frac{U_{IN}}{P_{IN}} \times V$$

Where C_{IN} is the renal clearance of inulin, U_{IN} and P_{IN} are respectively the concentrations of inulin in urine and plasma and V is the volume of urine produced per minute.

Biochemical estimations

PAH was determined in plasma and urine by the method of Dick and Davies (1949) and inulin by the method of Bacon and Bell (1947) using a double-beam spectrophotometer (Shimadsu UV-140).

Most of the plasma concentrations of PAH were 3–5 mg dl^{-1} and of inulin 20–50 mg dl^{-1}; most of the urine concentrations (after dilution to 1/100) were in the same range. Recovery experiments were performed between the ranges of PAH 0.3–9 mg dl^{-1} (86 individual recoveries) and inulin 3.3–90 mg dl^{-1} (98 individual recoveries). In these recovery experiments the standard deviation of the PAH measurements was ± 0.08 mg dl^{-1} and inulin ± 1.04 mg dl^{-1}.

Pa_{CO_2}, pH and P_{O_2} were determined using appropriate electrodes (IL LH) and blood-gas analyser (IL 213-227).

RESULTS

Acid-base state

Mean Pa_{CO_2} during "normocapnia" was 5.4 kPa (range 4.1–6.4 kPa); during hypocapnia the mean was 2.4 kPa (range 1.4–3.4 kPa).

Mean arterial pH during normocapnia was 7.28 (range 7.13–7.49) and during hypocapnia 7.46 (range 7.30–7.63). Using values for pK′ and solubility constant for carbon dioxide obtained from human blood and corrected for pH and temperature (Severinghaus, 1965) the mean actual bicarbonate concentration in hypocapnia was 13.5 mmol $litre^{-1}$ and during normocapnia 19 mmol $litre^{-1}$ ($P = 0.000043$; two-sided probability). Thus some of the experimental animals had a metabolic acidosis before the experimental period commenced and this became accentuated during hypocapnia (see below). It should be noted that all the samples were obtained after induction of anaesthesia.

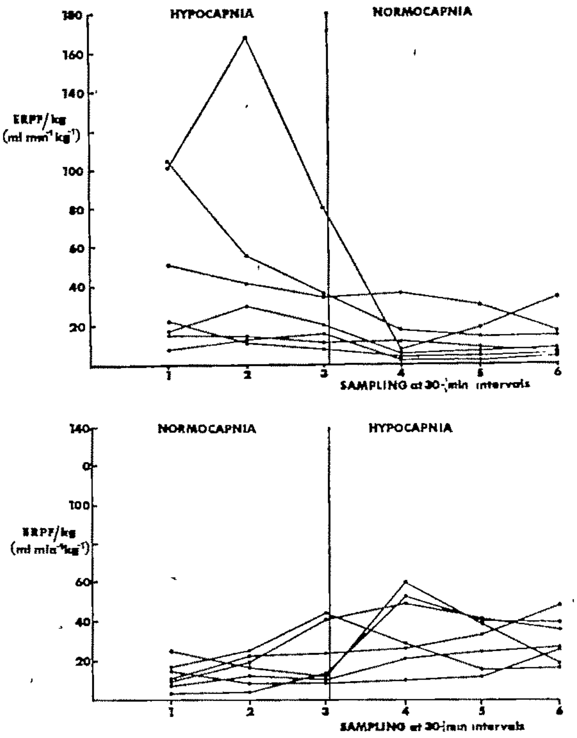

FIG. 1. The effect of an acute change in Pa_{CO_2} on estimated renal plasma flow. In half the experiments normocapnia preceded hypocapnia, and in the other half hypocapnia preceded normocapnia.

Renal function

In 13 of the 14 experiments an increase occurred in the ERPF and GFR during hypocapnia, associated with a reduction in RVR (figs 1 and 2, table I). ERPF, GFR and V increased approximately two-fold in hypocapnia, while renal vascular resistance decreased by approximately half.

The differences between ERPF, GFR and V in hypocapnia and normocapnia were statistically significant (table II) (paired t test).

Applying the Sign test to the values for ERPF, GFR and RVR, it was found that the effect produced

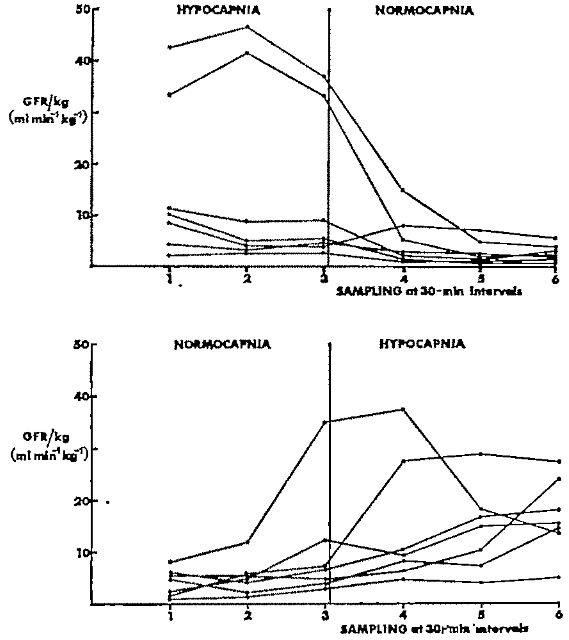

FIG. 2. The effect of an acute change in Pa_{CO_2} on glomerular filtration rate. In half the experiments normocapnia preceded hypocapnia, and in the other half hypercapnia preceded normocapnia.

by a change in Pa_{CO_2} in any one dog was of greater significance than any individual variation in the values between dogs (table II).

In the three experiments in which E_{PAH} was tested during hypocapnia the value obtained was at least 90%. The mean arterial pressures during the phases of the study are shown in table III.

DISCUSSION

There have been many studies on the effects of changes in P_{CO_2} on the renal aspects of acid–base state. Usually these studies have been on relatively long-term changes (Gennari, Goldstein and Schwartz, 1972), but some have been short-term (Simmons and Olver, 1965). There was a relatively recent study of the effect of hypercapnia on renal blood flow and other variables in the dog (Norman et al., 1970). There has, however, been no satisfactory study on the effects of low P_{CO_2} on renal blood flow and glomerular filtration rate.

Hypocapnia is induced frequently during anaesthesia and is common in patients undergoing artificial pulmonary ventilation in the intensive therapy unit. Thus, in two situations in which renal function

TABLE I. *Mean values for estimated renal plasma flow (ERPF), glomerular filtration rate (GFR), renal vascular resistance (RVR) and urine volume (V) for dogs during normocapnia and hypocapnia. Each mean is of three values in each of the 14 experiments. Note that hypocapnia preceded normocapnia in half the experiments. Units of renal vascular resistance are mm Hg per ml per min per 100 g kidney weight*

		ERPF (ml min^{-1} kg^{-1})	GFR (ml min^{-1} kg^{-1})	RVR	V (ml min^{-1})
Normocapnia (Pa_{CO_2} 5–5.5 kPa)		15.5	5.8	0.39	1.4
	SEM	2.4	1.1	0.16	0.2
	SD	9.2	4.2	0.61	1.1
Hypocapnia (Pa_{CO_2} 2–2.5 kPa)		36.7	14.5	0.17	3.2
	SEM	8.0	3.2	0.06	0.4
	SD	29.7	11.9	0.24	2.5

TABLE II. *Significance values obtained when the paired t test and Sign test were applied to the values for ERPF, GFR and RVR during hypocapnia and normocapnia.* t = *ratio of the mean of the sample to the standard error of the sample*

	ERPF (ml min^{-1} kg^{-1})	GFR (ml min^{-1} kg^{-1})	RVR (mm Hg ml^{-1} min^{-1} per 100 g kidney wt.)
Paired t test	$P = 0.002$** ($t = 3.841$)	$P = 0.0017$** ($t = 3.926$)	$P = 0.0001$*** ($t = 5.528$)
Sign test	$P = 0.013$*	$P = 0.057$	$P = 0.00024$***

TABLE III. *Values for mean arterial pressure (mm Hg) in each of the 14 experiments. The values given were obtained over a 2-min period around the time of blood sampling for PAH and inulin. In experiments 1–7 the change imposed was from hypocapnia to normocapnia and in 8–14 from normocapnia to hypocapnia*

Hypocapnia→normocapnia							Normocapnia→hypocapnia						
1	2	3	4	5	6	7	8	9	10	11	12	13	14
Hypocapnia							Normocapnia						
138	144	110	155	82	115	103	73	106	109	100	102	126	123
128	143	103	150	72	115	112	77	107	109	106	99	126	136
131	130	109	161	73	118	100	68	114	108	101	99	130	133
Normocapnia							Hypocapnia						
138	154	110	173	68	114	123	69	56	111	98	97	122	115
147	165	102	179	79	130	124	78	71	107	99	92	114	121
152	166	97	163	79	118	108	79	54	111	104	105	120	120

may be important, hypocapnia may occur and yet little is known about its effect on renal physiology.

In this study no observations were made for more than 1½ h after induction of anaesthesia to ensure that, as far as possible, there was a physiological steady state. Fentanyl was chosen as a supplement to nitrous oxide in maintaining anaesthesia because there is some evidence that in humans (when given together with droperidol) it produces less change in renal blood flow than inhalation agents (Gorman and Craythorne, 1966) which may cause a profound decrease in RBF and GFR (Bastrun and Deutsch, 1976). The technique used here appears to have less effect on ERPF and GFR than some methods of anaesthesia as shown by comparing the results in normocapnia with those of Houck (1948) in 75 conscious dogs. It may be seen (table IV) that the results are comparable, although there was a greater variation in the present study. The mean filtration fraction found in our study is within the normal range for dogs.

A technique of artificial pulmonary ventilation was chosen to maintain intrathoracic pressure more or less constant during normocapnia and hypocapnia. This is important because it has been found that an increase in intrathoracic pressure causes increased secretion of urine (Currie and Ullman, 1961).

Renal plasma flow may be estimated accurately using PAH only if E_{PAH} is 100%. Unfortunately, it was not found possible to estimate E_{PAH} in these experiments: three extraction ratios only were determined in hypocapnia; these were over 90%—that is, within the ratio regarded as normal in unanaesthetized dogs (Smith, 1951). It is known that at high renal blood flows, plasma extraction is decreased (Earley and Friedley, 1965) hence giving smaller plasma values and thus overestimating plasma clearance. These workers' observations, however, were made when saline loading was 50 ml min^{-1}; in the experiments reported here only 2 ml min^{-1} was administered (together with blood replacement).

The initial acid–base status of the experimental animals requires comment. Normal acid–base data for unanaesthetized dogs have been summarized (Altman and Dittman, 1964): the normal range of

TABLE IV. *A comparison between the mean, the SEM and SD of those values obtained for ERPF and GFR in the normocapnic anaesthetized dogs and those quoted for conscious dogs (Houck, 1948)*

	ERPF (ml min^{-1})		GFR (ml min^{-1})	
	Conscious dogs	Anaesthetized normocapnic dogs	Conscious dogs	Anaesthetized normocapnic dogs
Mean	13.5	15.5	4.29	5.8
SEM	0.375	2.4	0.115	1.1
SD	3.26	9.2	1.01	4.2

arterial blood pH for dogs has been described as 7.31–7.42 with $P\text{CO}_2$ 5.1 kPa (38 mm Hg). Using generally accepted values for pK′ and for the solubility constant of carbon dioxide determined in human blood (see above) the actual bicarbonate concentration derived from these data would be expected to be between 19 mmol litre^{-1} and 24 mmol litre^{-1}. The present results indicate that some of the experimental animals had a degree of metabolic acidosis initially. This is surprising since, although the dogs were kept in cages with a normal diet, they seemed well and gained weight during the duration of the experiments. The cause of this metabolic acidosis is being investigated. However, it may be that the acidosis occurred only during anaesthesia, although samples were not taken until after the animals had been anaesthetized for some time.

The metabolic acidosis does not seem to have influenced the findings. Changes in RBF, GFR and renal vascular resistance occurred in animals with or without a metabolic acidosis. Nevertheless, the existence of the acidosis in some of these experiments must be kept in mind when interpreting the results.

There is some doubt as to whether a small degree of metabolic acidosis develops during hypocapnia in the human (Utting, 1970). However, in the (extreme) degree of hypocapnia used in the dogs, the evidence is unequivocal. There was a smaller bicarbonate concentration during hypocapnia than during normocapnia.

There is evidence that the decrease in RBF which occurs during anaesthesia depends on the renin–angiotensin mechanism and that the decrease does not occur in dogs which have a large sodium intake or in which the renin–angiotensin system is blocked (Fray et al., 1976). The sodium balance of the experimental animals is, therefore, important. The fact that these animals were kept on a normal commercial diet would make it unlikely that there was any gross degree of electrolyte imbalance.

The duration of changes noted in this study is not known, since the experiments were relatively short. Preliminary results from current studies suggest that the changes observed here do not depend on the anaesthetic techniques used and occur during light anaesthesia with halothane.

It must be remembered that the studies were performed in animals with moderate diuresis. It is possible that the results may differ in animals with a different rate of urine production.

ACKNOWLEDGEMENTS

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EFFET DE L'HYPOCAPNIE AIGUE SUR CERTAINS ASPECTS DE LA FONCTION RENALE DE CHIENS ANESTHESIES

RESUME

On a provoqué l'hypocapnie sur des chiens légèrement anesthésiés à l'aide de protoxyde d'azote et de fentanyl. On a pris des mesures du débit estimé de plasma rénal (ERPF), du taux de filtration glomérulaire, de la résistance vasculaire et de la production d'urine. Pendant la (courte) durée de ces expériences on a trouvé que l'on pouvait associer l'hypocapnie à la ERPF laquelle était deux fois plus forte que celle qui se produit pendant la normocapnie, le taux de filtration glomérulaire et la production d'urine se trouvant augmentés par l'hypocapnie dans des proportions à peu près similaires, alors que la résistance vasculaire était réduite de moitié. Bien que certains des animaux servant aux expériences aient eu un certain degré d'acidose métabolique on ne pense pas que cela ait pu grandement influencer les résultats.

DIE WIRKUNG EINES AKUTEN KOHLENSAUREMANGELS IM BLUT AUF VERSCHIEDENE SEITEN DER NIERENFUNKTION IN NARKOTISIERTEN HUNDEN

ZUSAMMENFASSUNG

In leicht mit Lachgas und Fentanyl narkotisierten Hunden wurde ein Kohlensäuremangel im Blut herbeigeführt. Es wurden Messungen des geschätzten Nierenplasmaflusses (ERPF), der glomerularen Filtrierungsmenge, des Gefasswiderstandes und der Urinerzeugung durchgefuhrt. Während der (kurzen) Dauer der Versuche wurde festgestellt, dass der Kohlensäuremangel im Blut mit einem ERPF im Zusammenhang stand, der das Doppelte dessen wahrend eines normalen Kohlensäurevorkommens betrug. Die glomeruläre Filtrierungsmenge und Urinproduktion waren bei Kohlensäuremangel in annähernd gleichem Verhaltnis höher, während der Nierengefässwiderstand halbiert war. Obwohl bei einigen der Versuchstiere ein Mass Stoffwechselazidose auftrat, wurde deren Einfluss auf die Ergebnisse als nicht bedeutsam erachtet.

EFECTO DE LA HIPOCAPNIA AGUDA EN CIERTOS ASPECTOS DE LA FUNCION RENAL EN PERROS ANESTESIADOS

SUMARIO

Se indujo la hipocapnia en perros ligeramente anestesiados mediante fentanilo y óxido nitroso. Se llevaron a cabo mediciones del flujo plasmático renal estimado (FPRE), del ritmo de filtración glomerular, de la resistencia vascular y de la producción de orina. Durante el (corto) periode de los experimentos, se comprobó que la hipocapnia se asociaba con un FPRE doble del registrado durante la normocapnia. El ritmo de filtración glomerular y la producción de orina aumentaban por causa de la hipocapnia en una proporción aproximadamente similar, mientras que la resistencia vascular renal se reducía por mitad. Aunque algunos de los animales experimentales presentaran un grado de acidosis metabólica, se estimó que ello no influenciaba mucho los resultados.

Br. J. Anaesth. (1979), **51**, 733

CYTOTOXICITY OF I.V. ANAESTHETIC AGENTS ON THE ISOLATED RAT HEPATOCYTE

J. W. SEAR AND J. D. McGIVAN

SUMMARY

The isolated rat hepatocyte model has been used to assess the hepatotoxicity of a number of i.v. anaesthetic induction agents. Ketamine, Althesin and CCI 12923 (minaxolone) all inhibited gluconeogenesis and urea formation from alanine. There was also a decrease in the cell ATP concentration, and a dose-related increase in leakage of LDH. Of these indices of cell toxicity, gluconeogenesis from alanine was found to be the most sensitive. Fifty per cent inhibition of gluconeogenesis for all three agents occurred in the range 150–300 μmol. The effects of these agents on the isolated hepatocyte may be attributed to a primary impairment of mitochondrial function through a change in the ATP concentration. The plasma concentration of anaesthetic agents measured during their clinical use is at least one order of magnitude less than that required to cause 50% inhibition of gluconeogenesis.

Recently there has been a trend towards techniques of anaesthesia which avoid the use of the inhalation volatile anaesthetic agents. Several of these gaseous agents have been incriminated in the development of hepatic dysfunction and necrosis after operation (Sheenan, 1950; Bunker and Blumenfeld, 1963; Little and Wetstone, 1964; Becker, 1970). Total i.v. anaesthesia provides one method of avoiding these agents. There are no reports to date of any instances of clinical hepatic damage following either ketamine or Althesin administered as a continuous infusion. However, recent evidence has suggested that the use of ketamine by i.v. infusion may be associated with the occurrence after operation of abnormalities of certain hepatic function tests, namely those related to cellular enzyme leakage (Parke Davis, 1978—personal communication).

It has been shown previously that alphaxalone interferes with the process of oxidative phosphorylation in isolated mitochondria (Smith, Sweetman and Esmail, 1974). However, the use of a mitochondrial preparation removes many of the features of normal cellular and tissue architecture seen in the intact organ. The dose dependence of any effect observed in mitochondria is not necessarily of relevance in the intact organ, since hepatic accumulation of drugs may occur. The use of liver cells in culture or suspension has been advocated as an *in vitro* system for the assessment of the hepatotoxic potential of drugs. Among the agents shown to be toxic to freshly isolated rat hepatocytes in suspension have been certain of the halogenated volatile anaesthetics (Stacey, Priestly and Hall, 1978). We have adapted the same system to assess the cytotoxicity of some of the commonly used i.v. induction agents. We were also interested to compare the dose dependence of any cytotoxic effect with the plasma concentrations of the drugs found in clinical anaesthesia.

METHODS

Hepatocytes were prepared from 24-h fasted male Wistar rats of about 250 g weight by the method of Berry and Friend (1969) as modified by Krebs and others (1974). Viability of the cells was determined by Trypan Blue exclusion to be greater than 90%. The cell content of ATP was normally in the region of 10 nmol/mg of protein.

Cells were incubated in Krebs–Henseleit bicarbonate-buffered medium (Krebs and Henseleit, 1932) containing 2% w/v dialysed bovine albumin (fraction V) at pH 7.4 and 37 °C. Incubations were started by the addition of alanine (final concentration 10 mmol litre^{-1}) to the cell suspension containing the appropriate concentration of drug, and the cells were incubated with shaking at 37 °C in 95% oxygen and 5% carbon dioxide for the appropriate time interval. The incubations were terminated by the addition of perchloric acid (3.5% w/v final concentration). After removal of the protein by centrifugation, the acid extracts were neutralized with a small volume of KOH 3 mol litre^{-1} and used for metabolite assays. In

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experiments where the leakage of lactate dehydrogenase (EC 1.1.1.27) was measured, an aliquot of the cell suspension was centrifuged at 10 000 *g* for 5 s on the Eppendorf Zentrifuge model 3200, and lactate dehydrogenase activity was assayed in the supernatant fraction. Total lactate dehydrogenase activity was measured in an aliquot of the cell suspension which had been solubilized with Triton X-100 (0.5% w/v final concentration).

Glucose was assayed by the glucose oxidase method (Krebs et al., 1963). Urea was assayed as NH_3 by the method of Kirsten, Gerez and Kirsten (1963) after incubation of the sample with urease. ATP was determined using luciferase (Stanley and Williams, 1969). Lactate dehydrogenase activity was determined at 37 °C by the method of Bergmeyer, Bernt and Hess (1965). Cell protein was measured using a buiret method (Gornall, Bardawill and David, 1949).

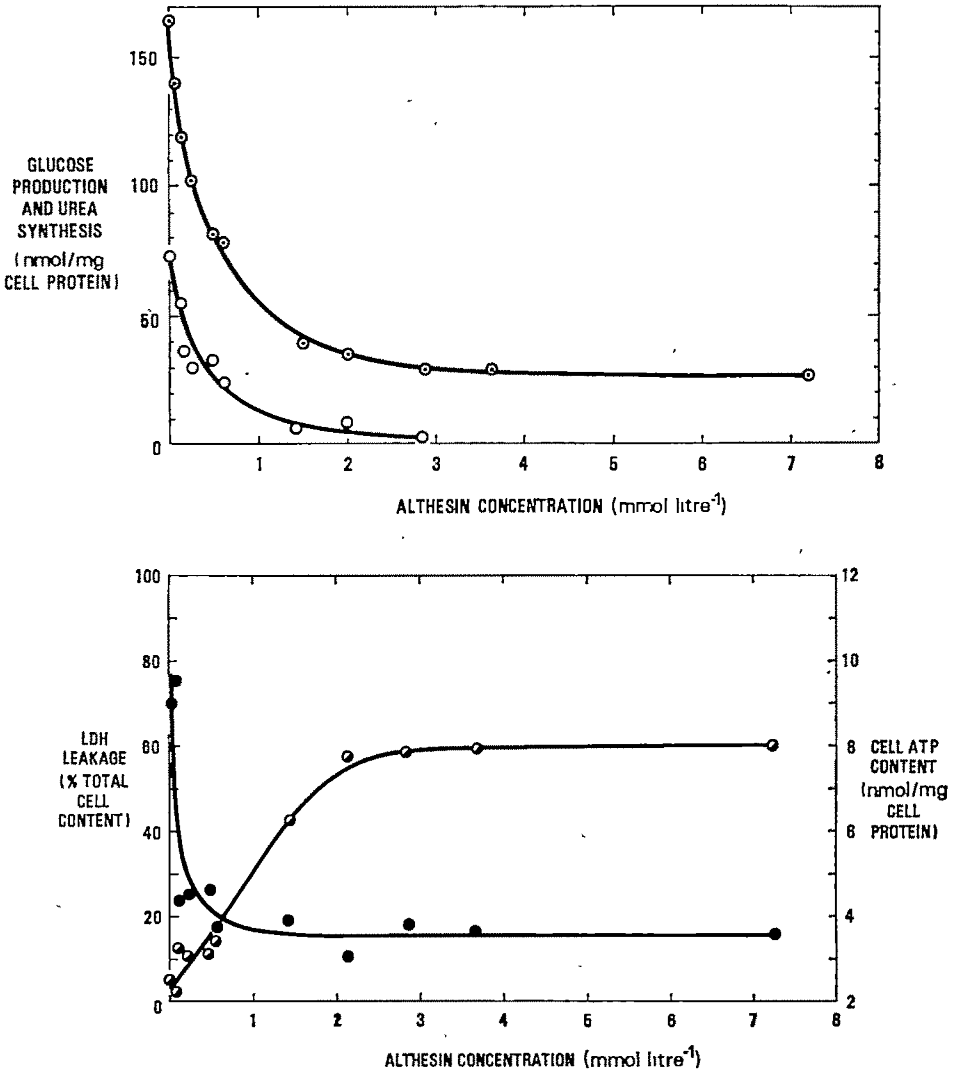

FIG. 1. Effect of Althesin on urea synthesis, gluconeogenesis, cell ATP content and LDH leakage in isolated liver cells. Cells were incubated at a final concentration of 3.6 mg protein/ml. Incubations were started by the addition of alanine 10 mmol litre^{-1}. After 40 min, samples were taken for LDH assays (◑), and the remainder of the suspension was deproteinized and used for assay of urea (⊙), glucose (○) and ATP (●). The results shown were obtained on a single batch of cells. Similar results have been obtained consistently in experiments of this type.

Drugs and reagents

Collagenase for the preparation of the isolated liver cells was purchased from C. F. Boehringer und Soehne, Mannheim. Bovine albumin was obtained from the Sigma Chemical Company. The i.v. agents (Althesin and ketamine) were as formulated for clinical use. Cremophor EL was supplied by Glaxo Research Laboratories Ltd. CCI 12923 (minaxolone) was kindly supplied for experimental use by Glaxo-Allenburys Research.

RESULTS

To investigate the cytotoxic effects of i.v. anaesthetic agents on isolated rat liver cells, the influence of these agents on the metabolism of alanine 10 mmol litre^{-1} was studied. In liver cells of starved rats, alanine is metabolized to form glucose and urea. In this system, the stoichiometry of glucose formation to urea synthesis is dependent on the presence or absence of added fatty acids (Krebs, Lund and Stubbs, 1976).

Figure 1 shows the effects of increasing amounts of Althesin on gluconeogenesis and urea synthesis from alanine 10 mmol litre^{-1}, and also on cell ATP concentration and lactate dehydrogenase (LDH) leakage after a 40-min incubation at 37 °C. Althesin caused a dose-dependent decrease in both gluconeogenesis and urea synthesis. Coupled with these effects, the cell ATP content decreased and the leakage of LDH was found to increase. Gluconeogenesis and urea synthesis are ATP-dependent processes and it is likely that the inhibition of these processes occurred as a result of a primary decrease in the cell ATP concentration brought about by the anaesthetic agents. It is known that gluconeogenesis is more inhibited by a decrease of the cell ATP concentration than is urea synthesis (Stubbs, Vignais and Krebs, 1978). Althesin appears to exert a general cytotoxic effect on the isolated hepatocyte which is manifest as an induction of membrane leakage, a decrease in cell ATP concentration and a consequent reduction in the rate of intermediary metabolism. In similar experiments (not shown), minaxolone and ketamine were shown to exert similar cytotoxic effects. Of the measurements made, gluconeogenesis appeared to be the most sensitive index of cell toxicity. Accordingly in subsequent experiments, gluconeogenesis from alanine was chosen for investigation.

Figure 2 shows the time courses of glucose production from alanine in the presence of minaxolone, ketamine and the uncoupling agent carbonyl cyanide meta-chloro-phenyl hydrazone (Cl-CCP). In the absence of inhibitors, glucose synthesis was linear over a 40-min period. The addition of intermediate amounts of minaxolone and ketamine at zero time caused a dose-dependent lag in glucose production and a reduction in the overall rate after the lag period.

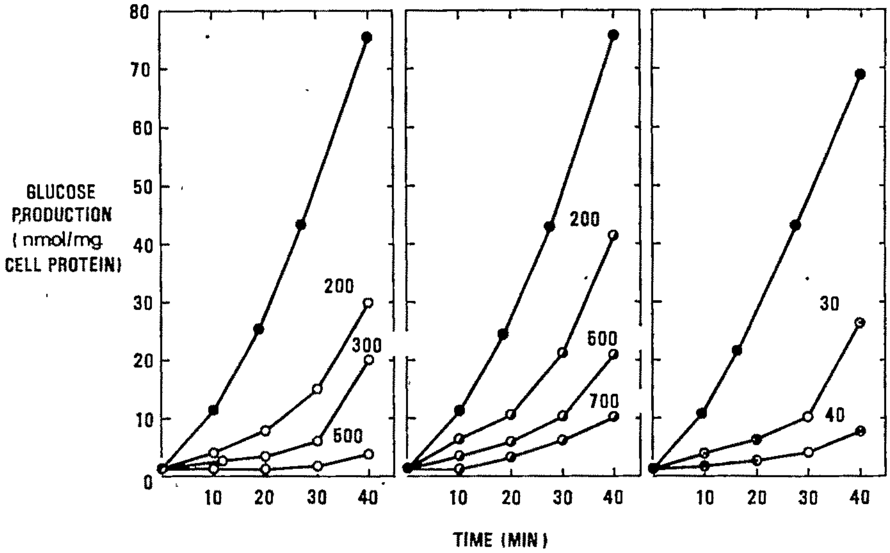

FIG. 2. Time course of gluconeogenesis from alanine 10 mmol litre^{-1} in the presence of minaxolone, ketamine and Cl-CCP. Cells (2–5 mg protein/ml) were incubated with alanine 10 mmol litre^{-1} plus various concentrations (μmol litre^{-1}) of inhibitors as shown. Aliquots were assayed for glucose at 10-min intervals. Control (●); minaxolone (○); ketamine (◑); and Cl-CCP (⊙).

At large concentrations of the two agents (greater than 500 μmol litre^{-1} for each), glucose synthesis was inhibited almost completely. Similar time courses were observed with increasing concentrations of the uncoupling agent Cl-CCP, which specifically inhibits mitochondrial ATP synthesis (Heytler and Prichard, 1962).

These results are consistent with a primary effect of the anaesthetic agents on cell ATP concentrations, and hence their action is reflected in the rate of gluconeogenesis. From these time courses, it is seen that the largest percentage differences in glucose production in the presence of intermediate concentrations of anaesthetic agent occurred between 30 and 40 min. Studies with the other steroid agent, Althesin, showed a similar dose-dependent time course of inhibition. The solvent used in the formulation of of Althesin, Cremophor EL, did not inhibit glucose synthesis from alanine in this system.

In figure 3, the ATP concentration after 40 min of incubation has been plotted against glucose production after this time in the presence of varying concentrations of anaesthetic agent or uncoupler. Both axes of the graph are expressed as per cent of the value of the measurement in the absence of added inhibitor. A positive correlation was observed ($r = 0.63$, $P < 0.01$, $n = 34$ observations) when the data for Althesin, ketamine and minaxolone were plotted. These results provide further evidence consistent with a primary effect of all these agents on cell ATP synthesis, rather than any specific effect on gluconeogenesis.

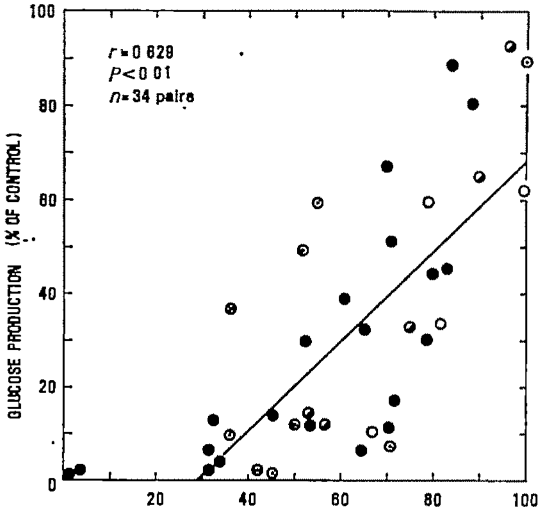

FIG. 3. Correlation between cell ATP content and gluconeogenesis from alanine 10 mmol litre^{-1}. Cells were incubated with alanine 10 mmol litre^{-1} in the presence of varying concentrations of minaxolone, ketamine, Althesin and Cl-CCP. The cell ATP content and glucose production were measured after 40 min. ATP content is expressed as a percentage of that present in the absence of inhibitors. Glucose production is similarly expressed as a percentage of that present in the absence of inhibitors. The results shown were obtained from experiments on five separate batches of cells. Ketamine (○); minaxolone (●); Althesin (○); and Cl-CCP (◑). The value for r was obtained from 34 paired data for ketamine, minaxolone and Althesin.

With this model system, it is possible to compare the relative cytotoxic effects of varying concentrations of different i.v. anaesthetic agents (fig. 4). It can be seen that the three anaesthetic agents studied are approximately equally effective in inhibiting gluconeogenesis. The concentration causing 50% inhibition of gluconeogenesis for each drug lies in the range 150–300 μmol litre^{-1}.

DISCUSSION

The effects of halothane and other volatile inhalation anaesthetic agents on liver function have been studied extensively using the isolated perfused rat liver (Biebuyck, Lund and Krebs, 1972). The inhibitory action of halothane on liver metabolism was shown to be a primary interference with mitochondrial ATP synthesis. Gluconeogenesis from lactate 10 mmol litre^{-1} was affected less by the addition of ketamine 365 μmol litre^{-1} than by halothane (2.5% v/v). In the present study, we have chosen to use suspended isolated rat hepatocytes as the model system.

Isolated liver cells in culture or in suspension have been used to study the cytotoxic effects of a number of drugs (Zimmerman and Kendler, 1970; Zimmerman, Kendler and Libber, 1973; Zimmerman et al., 1974; Abernathy, Lukacs and Zimmerman, 1975; Goto et al., 1976; Dujovne et al., 1970). The main index of cell function and integrity used by these authors to assess the cytotoxic effects of the drugs under investigation was cellular enzyme leakage.

The criteria available for the assessment of the viability of isolated liver cells in suspension have been discussed by Baur, Kasperek and Pfaff (1975). In the present study, several of these criteria have been measured simultaneously as a function of the added drug concentration. Of these, ATP concentration within the cell and gluconeogenesis from alanine appear to be the most sensitive. The production of glucose by gluconeogenesis has the merit of being easy to assay, and is relatively inexpensive. However, it should be noted that it is necessary to use starved rats in order to study gluconeogenesis. In the fed rat,

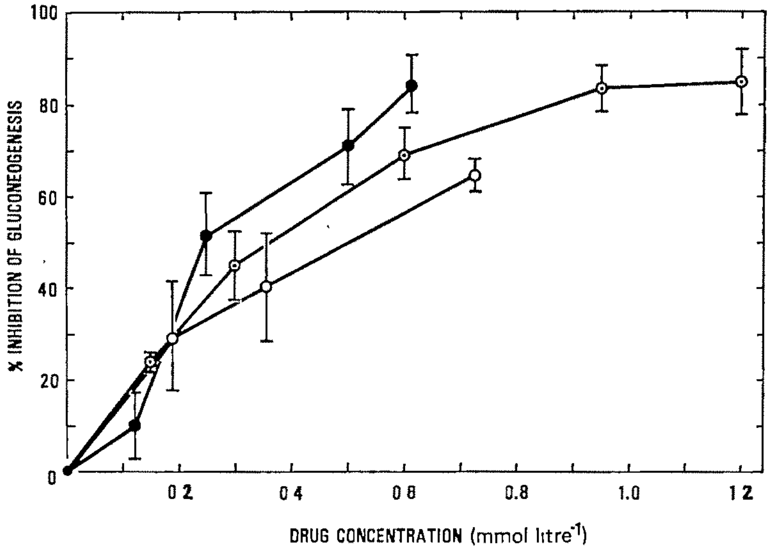

FIG. 4. Concentration dependence of the inhibition of gluconeogenesis by ketamine, minaxolone and Althesin. Cells were incubated with alanine 10 mmol litre^{-1} plus varying amounts of inhibitors for 40 min. The results are expressed as the percentage inhibition of the control rates. The results are presented as mean ± SEM of observations on eight separate batches of cells. Ketamine (○); minaxolone (●); and Althesin (⊙).

breakdown of endogenous glucogen interferes with the assay of glucose synthesis from alanine. Although enzyme leakage is a commonly measured index of cell viability, it will be seen that gluconeogenesis is half-maximally inhibited at drug concentrations which cause only relatively small increases in LDH leakage (fig. 1).

The present study has shown that the i.v. anaesthetic agents cause a dose-dependent reduction in the cell ATP content. Smith, Sweetman and Esmail (1974) showed that alphaxalone (the major component of Althesin) had two effects on ATP synthesis in isolated rabbit brain and rat liver mitochondria. At small concentrations (70 μmol litre^{-1}) there was an inhibition of electron transport between NADH and cytochrome b, while at larger concentrations (alphaxalone 333 μmol litre^{-1}) there was uncoupling of oxidative phosphorylation. The results obtained using isolated hepatocytes in suspension are consistent with the possibility that the primary effect of the i.v. anaesthetic agents is at the level of mitochondrial ATP synthesis. The concentrations of Althesin, ketamine and minaxolone required in the present study to inhibit gluconeogenesis by 50% are in the range 150–300 μmol litre^{-1}.

The albumin in the cell suspension medium may itself bind some of the added anaesthetic agents. This may partially explain the slightly larger concentrations of alphaxalone needed to cause 50% inhibition of gluconeogenesis in the cell suspension, compared with the concentrations required to uncouple mitochondria (Smith, Sweetman and Esmail, 1974). On the assumption that the action of alphaxalone is primarily on mitochondrial function, it would seem that this drug is not actively accumulated by liver cells. If massive accumulation occurred in the hepatocyte, the concentration of drug required to inhibit cell metabolism would be less than that required to impair the function of isolated mitochondria. However, it should be noted that isolated cells prepared by this method are capable of accumulating certain amino acids (Le Cam and Freychet, 1977; Joseph, Bradford and McGivan, 1978).

The concentrations of anaesthetic agents added to the hepatocytes in suspension are in excess of those measured in the plasma of both the rat and man. Following administration of a single sleep dose of Althesin to man, peak plasma concentrations of alphaxalone are of the order of 2 μg ml^{-1} (6 μmol litre^{-1}) (Dubois, Allison and Geddes, 1975). Similar plasma alphaxalone concentrations have been measured in human plasma after infusions of Althesin (Sear and Prys-Roberts, 1978). Plasma concentrations of minaxolone between 1 and 3 μg ml^{-1} have been detected in the rat after both single doses and continuous infusions. In both the single dose and infusion groups, the plasma concentration varied with both the dose administered and the infusion rate (Glaxo–Allenbury's Research Ltd, data on file). The administration of single doses of ketamine, sufficient to cause sleep in either man or the rat, is associated with plasma concentrations of the drug of up to 10 μmol $litre^{-1}$ (Chang and Glasko, 1972; Cohen et al., 1973). During infusions of ketamine in man, Idvall and colleagues have measured plasma concentrations in the range 5–15 μmol $litre^{-1}$ (Idvall et al., 1978).

Although the *in vitro* isolated cell preparation may not act identically to the intact organ, the results of our study would suggest an inherent safety margin of at least 10-fold during the clinical use of these i.v. anaesthetic agents.

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CYTOTOXICITE DES AGENTS ANESTHESIANTS ADMINISTRES PAR VOIE INTRAVEINEUSE SUR L'HEPATOCYTE ISOLE DU RAT

RESUME

On a utilisé le modèle de l'hépatocyte isolé du rat pour évaluer l'hépatotoxicité d'un certain nombre d'agents d'induction d'anesthésie administrés par voie intraveineuse. La kétamine, l'althésine et le CCI 12923 (minaxolone) ont tous inhibé la gluconéogénèse et la formation d'urée à partir de l'alanine. Il y a aussi eu une diminution des concentrations d'ATP dans les cellules et une augmentation de la fuite de LDH qui a été fonction de la dose. Sur ces indices de la toxicité des cellules, on a trouvé que la gluconéogénèse à partir de l'alanine a été la plus sensible. Cinquante pour cent de l'inhibition de la gluconéogénèse pour ces trois agents s'est produite dans la plage de 150–300 μmol. Les effets de ces agents sur l'hépatocyte isolé peuvent être attribués à un affaiblissement primaire de la fonction mitochondriale du fait d'une variation dans la concentration d'ATP. La concentration d'agents anesthésiants dans le plasma mesurée pendant leur usage clinique est au moins d'un ordre de grandeur inférieur à celui qui est requis pour provoquer 50% de l'inhibition de la gluconéogénèse.

DIE ZELLENGIFTIGKEIT VON INTRAVENÖSEN NARKOSEMITTELN BEI DER ISOLIERTEN LEBERZELLE DER RATTE

ZUSAMMENFASSUNG

Das Modell der isolierten Leberzelle der Ratte wurde dazu benutzt, die Lebertoxitizität einer Anzahl intravenöser Narkosemittel zu beurteilen. Ketamin, Althesin und CCI 12923 (Minaxolen) hatten alle eine hemmende Wirkung auf die Glykoseneubildung und die Harnstoffbildung aus Alanin. Dies war mit einem Abfall in der Konzentration an Zellen-ATP und einem dosisbezogenem Anstieg im Durchsickern von LDH verbunden. Es wurde festgestellt, dass von diesen Zellentoxitizitätsanzeichen die Glykoseneubildung aus Alanin am empfindlichsten reagierte. Eine fünfzigprozentige Hemmung der Glykoseneubildung trat bei allen drei Mitteln im Bereich 150–300 μmol ein. Die Einwirkung dieser Mittel auf die isolierte Leberzelle kann einer primären Störung der Mitochondrienfunktion durch eine Veränderung in der ATP-Konzentration zugeschrieben werden. Die während ihrer klinischen Anwendung gemessene Plasmakonzentration von Narkosemitteln ist um mindestens eine Grössenmordnung geringer, als die, die zum Hervorrufen einer 50-prozentigen Hemmung der Glykoseneubildung erforderlich ist.

CITOTOXICIDAD DE LOS AGENTES ANESTETICOS I.V. EN EL HEPATOCITO AISLADO DEL RATON

SUMARIO

El modelo de hepatócito aislado del ratón se usó para evaluar la hepatotoxicidad de una serie de agentes de inducción anestética i.v. La quetamina, la altesina y el CCI 12923 (minaxolona) inhibieron todos gluconeogénesis y formación de úrea a partir de la alanina. También se produjo una reducción en la concentración ATP de las células, y un aumento de la fuga de LDH relacionado con la dosis. Entre estos índices de toxicidad celular, la gluconeogénesis a partir de la alanina demostró ser la más sensitiva. Ocurrió una inhibición del 50% de gluconeogénesis para cada uno de los tres agentes en la escala de 150–300 μmol. Los efectos de estos agentes en el hepatócito aislado pueden atribuirse a un deterioro primario de la función mitocondrial a través de un cambio de la concentracion ATP. La concentración plasmática de los agentes anestéticos medidos durante su uso clínico es por lo menos de un orden de magnitud inferior al que se requiere para causar una inhibición del 50% de gluconeogénesis.

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PHARMACOKINETICS OF FENTANYL AS A POSSIBLE EXPLANATION FOR RECURRENCE OF RESPIRATORY DEPRESSION

H. STOECKEL, J. H. HENGSTMANN AND J. SCHÜTTLER

SUMMARY

The pharmacokinetics of fentanyl are complicated by an additional increase in plasma concentration during the elimination phase of the drug. We have confirmed that fentanyl is excreted in the gastric juice and reabsorbed from the alkaline medium of the small intestine. In addition, the stomach wall in rats has an important storage capacity for fentanyl. A maximum of about 20% of the dose was found in the stomach wall after i.v. injection. In man the resected part of the stomach contained 16% of the dose, 10 min after injection. These observations could be important in explaining the occurrence of respiratory depression in the period after operation.

Becker and others (1976) reported biphasic respiratory depression after fentanyl was used to supplement nitrous oxide anaesthesia. Adams and Pybus (1978) reported three patients who suffered severe respiratory depression after apparent recovery from a general anaesthetic which included fentanyl; this was treated successfully with naloxone.

We have investigated the disposition of fentanyl in patients who received fentanyl during the course of clinical anaesthesia.

METHODS

Fentanyl was obtained as the citrate salt in 10-ml vials as available commercially. Doses and concentrations given refer to the free base. Concentrations of fentanyl in biological material were determined by radioimmunoassay (Michiels, Hendriks, and Heykants, 1977). The coefficient of variation was ±5% for a concentration of 1 ng ml^{-1} (0.97 ± 0.05 ng ml^{-1}) and ±10.2% for a 5-ng ml^{-1} sample.

Seven patients undergoing abdominal hysterectomy gave informed consent to the study. Premedication comprised promethazine 50 mg and atropine 0.5 mg, i.m. 1 h before operation. Anaesthesia was induced with methohexitone 1 mg kg^{-1}. Suxamethonium 1.5 mg kg^{-1} was given to facilitate tracheal intubation. Anaesthesia was maintained with 1.0% halothane, and 60% nitrous oxide in oxygen. Myoneural blockade was maintained with pancuronium bromide (total dose 6 mg). The lungs were ventilated artificially with a semi-closed system (Spiromat 650, Drager). A bolus dose of fentanyl 0.5 mg was given into a forearm vein immediately following tracheal intubation. Blood was sampled through a plastic cannula at 2, 5, 7, 10, 15, 20, 30, 45, 60, 90 and 120 min after injection. Gastric juice was aspirated through a gastric tube after filling the stomach with 200 ml of physiological saline at 37 °C.

In five healthy male volunteers, age range 24–32 yr, an aqueous solution of 0.3 mg of fentanyl base was administered orally after an overnight fast. Venous blood was sampled from a forearm vein at 15, 30, 45, 60, 75, 90, 120, 180 and 240 min after ingestion.

Three dogs (average weight 15 kg) were anaesthetized with pentobarbitone 15 mg kg^{-1}. After laparotomy the pylorus was ligated and oesophageal reflux was prevented by a Sengstaken–Blakemore probe. At 5, 10, 20, 30, 40, 50, 60 and 90 min after i.v. injection of fentanyl 0.25 mg the stomach was flushed with acidified (pH 3.0) physiological saline.

For the determination of fentanyl concentration in brain, lungs and stomach wall, 20 female Sprague–Dawley rats received fentanyl 5 μg per 100 g body weight into the tail vein. After a short period of intermittent compression of the chest wall, animals in groups of five were decapitated at 10, 20, 40 and 80 min. The organs were removed and homogenized in 2 × 5 ml of absolute methanol. After 12 h at 4 °C the protein was spun down by centrifugation. The methanolic supernatant was diluted 1 : 5 with phosphate buffer 0.05 mol litre^{-1} (pH 7.4).

Recovery from organ homogenates was determined after addition of 50 000 counts ^{3}H-fentanyl (= 1 ng) to the brain, lungs and stomach of five rats. After

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homogenization, 75% of the radioactivity was recovered in the supernatant of lungs and stomach and 85% in brain. Our results are not corrected for this recovery rate.

This same procedure was carried out for tissue samples of the resected part of human stomach in six patients who received fentanyl base 0.5 mg during general anaesthesia for Billroth II gastrectomy. Regression analysis for the individual time–log. concentration pairs was by the method of least squares.

RESULTS

Patient study

Large initial plasma fentanyl concentrations were observed following a bolus dose of 0.5 mg (50–100 ng ml^{-1}). In many patients a secondary increase in plasma concentration was seen, but the time course of the changes was variable. Peak concentrations occurred 20–90 min after injection (figs 1 and 2). Furthermore, the area under the curve of these secondary peaks differed considerably.

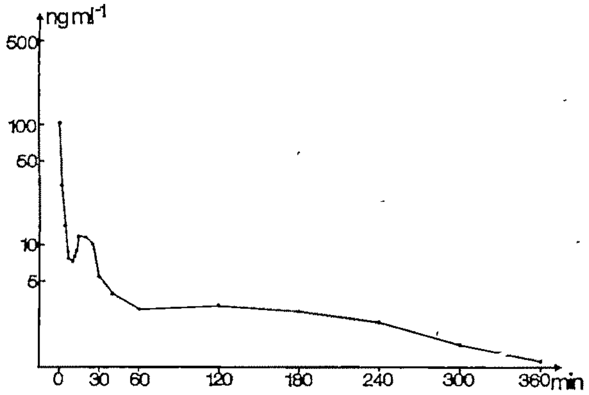

FIG. 1. Serum fentanyl concentrations following a dose of 0.5 mg i.v. in a single patient.

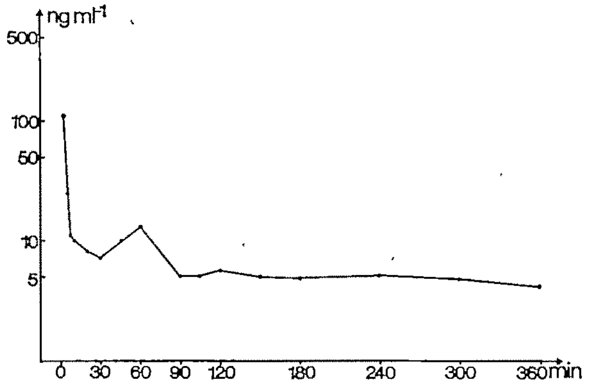

FIG. 2. Serum fentanyl concentrations following a dose of 1.6 mg i.v. in a single patient.

Following oral administration of fentanyl 0.3 mg in aqueous solution a peak plasma concentration occurred at about 90 min (fig. 3). The area under the curve (corrected for the dose administered) was about one-third of that following i.v. injection (767 *v.* 2417 ng ml^{-1} min) indicating reduced enteric absorption after ingestion.

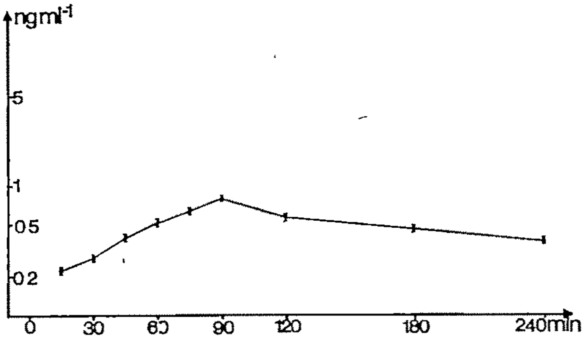

FIG. 3. Serum concentrations of fentanyl in five patients following an oral dose of 0.3 mg (mean ± 1 SD).

The concentration of fentanyl in gastric juice was determined in seven patients following a bolus injection of fentanyl. A typical example is demonstrated in figure 4. During the rapid reduction in plasma concentrations, fentanyl up to 400 ng min^{-1}

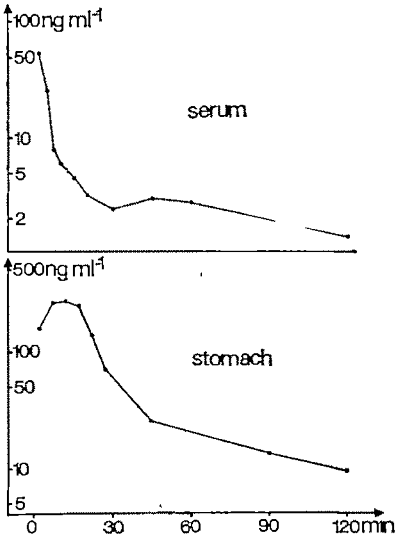

FIG. 4. Serum (upper) and gastric juice (lower) concentrations of fentanyl in one patient following fentanyl 0.5 mg i.v.

was detected in the gastric juice. The total amount secreted in gastric juice was estimated as 3–4% of the injected dose. However, a loss of gastric juice during the collection periods was suspected because of the inflection in the plasma concentration curve.

In patients undergoing surgery for gastrectomy it was not possible to set a time interval between injection of fentanyl and isolation of the stomach from the circulation. The time intervals varied from 34 to 105 min. Assuming linear elimination kinetics for the stomach wall, it is possible to calculate by regression analysis the amount of fentanyl within this organ. A regression coefficient (r) of 0.91 revealed a good fit for the calculated curve. Using the equation for this regression line (fig. 5), we calculated that about 16% of the dose was located in the stomach 10 min after injection.

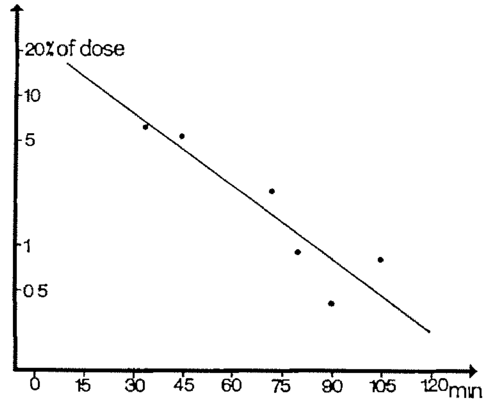

FIG. 5. Amount of fentanyl in the human stomach wall as calculated from the concentrations in representative parts of resected material. For the calculation of the total amount an average weight of 500 g was assumed. The abscissa represents the time between the injection of 0.5 mg of the drug and the removal of the organ.

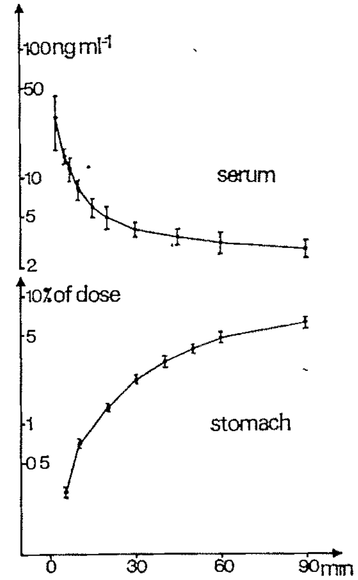

FIG. 6. Serum concentrations (upper) and gastric secretory rates (lower) of fentanyl in three dogs with a ligated stomach after fentanyl 0.25 mg i.v. (mean ± 1 SD).

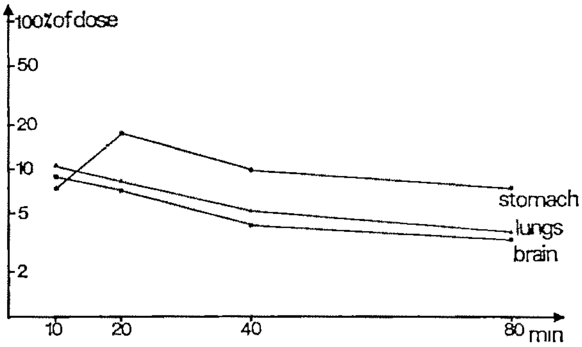

FIG. 7. Amount of fentanyl in the stomach, lungs and brain of the rat following an i.v. dose of fentanyl 5 μg per 100 g body weight (mean values).

Animal study

After bolus i.v. injection of fentanyl 0.25 mg in dogs the decay of plasma concentrations was that of a two-compartment open model. There was no secondary increase during the 2 h of the experiment. When the gastric outlet was closed the cumulative amount of fentanyl in gastric juice was approximately 10% of the dose when extrapolated to infinity (fig. 6).

The concentrations of fentanyl in the rat organ homogenates of brain and lungs decreased from the first determination at 10 min. The concentration in the stomach wall reached a maximum at 20 min corresponding to approximately 20% of the dose. Even at the latest point determined (80 min), 10% of the dose still remained within the stomach (fig. 7).

DISCUSSION

In most of our patients, plasma concentrations of fentanyl could be analysed according to a two-compartment open model (Hess, Stiebler and Herz, 1972) described for tritiated fentanyl. In some patients, however, variations could be seen (figs 1 and 2) and when we shortened the interval between blood collections, nearly all the patients investigated showed a secondary increase in plasma concentration of fentanyl.

A possible explanation for this phenomenon is an entero-systemic recirculation as described by Schanker and others (1958) for basic drugs in general, by Trudnowski and Gessner (1975) for pethidine and by Lynn and others (1976) for methadone. Therefore, we studied gastric secretion and absorption of fentanyl from the gut in man.

The most likely moment for the appearance of fentanyl in gastric juice would be immediately following injection, when the greatest concentration gradient occurs between blood and stomach wall and gastric juice. Our studies showed an increasing concentration of fentanyl in the gastric juice of man up to 30 min after i.v. injection. The gastric excretion rates decreased thereafter approximately in parallel with the serum concentrations.

Calculation of the amount of fentanyl secreted into gastric juice was not exact because of the difficulty in ensuring complete collection of juice.

In the dog, with a ligated pylorus, as much as 7% of the i.v. dose could be collected in gastric juice. Extrapolation to infinity revealed a cumulative amount of about 10% of the dose. However, this may be less than that observed in man because the plasma concentrations in the dog following the injection of the drug even in large doses (0.02 *v.* 0.01 mg kg^{-1}) were not as great as in man.

The stomach wall both secretes and stores fentanyl. About 20% of the dose was located in the stomach wall at 20 min after injection, a value twice that in lung and brain. In man, storage was also demonstrated by extrapolation of data from random samples of human stomach wall in six patients. We calculated that about 16% of the dose was retained in the stomach wall.

We demonstrated that fentanyl was secreted into gastric juice after i.v. injection. In man the measurement of plasma concentrations following an oral dose of fentanyl revealed absorption from the gut, but with an availability of only 33%. The total amount absorbed (amount secreted reduced by the bioavailability factor) was calculated to be about 5% of the injected dose.

The time of onset and the extent of this mechanism may limit the pharmacological effects in patients. This additional amount of fentanyl may be negligible when compared with the total dose injected. However, at the time of appearance of the reabsorbed fentanyl, at about 30–60 min, more than 75% of the injected dose is located in the peripheral compartment (Hengstmann, Stoeckel and Schüttler, 1978). The pharmacokinetic properties imply a rapid transfer of drug into the peripheral compartment of the two-compartment open model. This amount, together with the amount entering the compartment after reabsorption, may be sufficient to cause acute respiratory insufficiency or reduced sensitivity of the chemoreceptors to carbon dioxide. This may occur even at 4 h after drug injection (Becker et al., 1976) when only about 20% of the dose is stored in the peripheral tissues (Stoeckel et al., 1979). The significance of this concept can only be judged from simultaneous measurement of plasma concentrations and testing for possible respiratory depression following fentanyl analgesia.

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PHARMACOCINETIQUE DU FENTANYL EN TANT QU'EXPLICATION POSSIBLE DE LA REPETITION DE LA DEPRESSION RESPIRATOIRE

RESUME

La pharmacocinétique du fentanyl est compliquée par l'augmentation supplémentaire des concentrations dans le plasma qui se produisent pendant la phase éliminatoire de ce médicament. Nous avons confirmé que le fentanyl s'éliminait dans le suc gastrique et était réabsorbé par la substance alcaline de l'intestin grêle. De plus, la paroi stomacale des rats a une capacité importante de stockage du fentanyl. On a trouvé un maximum de 20% environ de la dose dans la paroi stomacale après injection intraveineuse. Chez l'homme, la résection d'une partie de l'estomac a fait ressortir qu'il contenait 16% de la dose, 10 mn après l'injection. Ces observations pourraient être importantes pour expliquer l'apparition de dépression respiratoire au cours de la période qui suit l'intervention chirurgicale.

DIE PHARMAKOKINETIK VON PENTANYL ALS MÖGLICHE ERKLÄRUNG FÜR DAS WIEDERAUFTRETEN VON RESPIRATORISCHER DEPRESSION

ZUSAMMENFASSUNG

Das lineare pharmakokinetische Verhalten von Fentanyl wird durch ein Wiederansteigen der Blutspiegel wahrend der Eliminationsphase dieses Pharmakons gestort. Wir stellten fast, dass das basische Fentanyl in den Magen sezerniert wird und vom alkalischen Dünndarmmilieu reabsorbiert wird. Darüberhinaus besitzt auch die Magenwand eine erhebliche Speicherkapazitat fur das Pharmakon Fentanyl. Bei Ratten fanden wir 20% der intravenos applizierten Dosis in der Magenwand. Im resezierten Magenanteil von Patienten nach Billroth II Magenresektion fanden wir 16% der applizierten Fentanyldosis 10 Min nach Injektion. Diese Beobachtungen bieten sich als mögliche Erklärung für das Wiederauftreten der Atemdepression nach Ende der klinischen Fentanylanästhesie an.

FARMACOCINETICA DEL FENTANILO COMO POSIBLE EXPLICACION DE LA RECURRENCIA DE DEPRESION RESPIRATORIA

SUMARIO

La farmacocinética del fentanilo se complica por un aumento adicional en la concentración plasmática durante la fase de eliminación de la substancia. Confirmamos que el fentanilo se excreta en los jugos gástricos y se reabsorbe a partir del medio alcalino del intestino delgado. Además, la pared estomacal en los ratones posee una importante capacidad de almacenamiento de fentanilo. Se encontró un máximo del 20% aproximadamente de la dosis en su pared estomacal después de una inyección i.v. En el hombre, la parte reseccionada del estómago contenía un 16% de la dosis, 10 min después de la inyección. Estas observaciones podrían revestir importancia para explicar la ocurrencia de depresiones respiratorias en el período post-operatorio.

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EFFECTS OF ANAESTHESIA AND SURGERY ON PLASMA ALDOSTERONE CONCENTRATION AND RENIN ACTIVITY IN MAN

T. OYAMA, K. TANIGUCHI, T. JIN, T. SATONE AND T. KUDO

SUMMARY

The effects of various anaesthetic agents and surgery on the plasma concentrations of aldosterone and on renin activity were investigated in 76 patients. The plasma concentration of aldosterone was increased markedly by 2.5 times the control value during 45 min of ether anaesthesia. It was increased also during halothane, methoxyflurane and enflurane anaesthesia. Spinal anaesthesia did not alter significantly the plasma concentration of aldosterone. Plasma renin activity and ACTH concentration were increased slightly during general anaesthesia.

The present study was undertaken to investigate the effects of various anaesthetic agents and surgery on the plasma concentrations of aldosterone and the renin activity in man.

The renin–angiotensin–aldosterone system plays an important role in the maintenance of electrolyte balance, fluid volume and arterial pressure. Anaesthetics have been reported to cause the release of renin in rats as measured by plasma renin activity (Pettinger et al., 1975; Miller, Ackerly and Peach, 1978). However, such increases have not been observed in man (Robertson and Michelakis, 1972; Bailey et al., 1975; Miller et al., 1975). Furthermore, no extensive study has reported on the effect of anaesthetics on the plasma concentrations of aldosterone in man apart from our previous study which featured a small number of patients (Oyama et al., 1973).

MATERIALS AND METHODS

Seventy-six patients, in the age range 10–58 yr, were studied after giving informed consent. None had a history of endocrine disease, or of hepatic or renal malfunction. The patients were all in good general health. Premedication consisted of pentobarbitone 100 mg given orally, and pethidine 35 mg i.m. plus atropine 0.5 mg i.m. No food or water was given for at least 10 h before the start of anaesthesia.

The effects of ether–nitrous oxide anaesthesia (16 patients), halothane–nitrous oxide (15 patients), methoxyflurane–nitrous oxide (15 patients), enflurane–nitrous oxide (15 patients), spinal anaesthesia (15 patients) and of surgery on the plasma concentrations of aldosterone were determined in 76 surgical patients. With the exception of the spinal anaesthesia group (10–15 min) the patients were anaesthetized for 45 min before the start of surgery. Hysterectomy was performed in the majority of patients except for those in the spinal anaesthesia group, who underwent appendicetomy or haemorrhoidectomy.

The plasma renin activity (PRA), serum and urinary concentrations of sodium and potassium, urinary Na/K ratios and urine volume were determined simultaneously in all groups. Plasma concentrations of ACTH were measured in 33 patients who underwent halothane–nitrous oxide, enflurane–nitrous oxide anaesthesia and spinal anaesthesia.

Anaesthesia was induced and maintained with methoxyflurane 0.3–1% or diethyl ether 5–15%, or enflurane 1.0–3.0% combined with nitrous oxide 3.5 litre min^{-1} in oxygen 1.5 litre min^{-1}, and tubocurarine was given to produce neuromuscular blockade when required. Thiopentone was not used as an induction agent in any patient. Intubation of the trachea was performed following the injection of suxamethonium 40 mg i.v. Ventilation of the lungs was assisted manually throughout the procedure.

To produce spinal anaesthesia amethocaine 10–12 mg diluted with 10% glucose 2 ml was injected into the subarachnoid space at either L3–4 or L4–5. The level of anaesthesia, determined with pinprick, was T10–6 and its duration was 90–120 min (mean 105.3 ± 3.1 SEM). The duration of surgery was 12–30 min (mean 22.2 ± SEM 1.7).

Low molecular weight dextran 500 ml was infused throughout the procedure in each group, and whole blood was transfused when blood loss exceeded 300 ml.

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Four 6-ml samples of venous blood were drawn into heparinized syringes in the general anaesthesia groups: (1) at 8.30 a.m., immediately before induction of anaesthesia; (2) 45 min after anaesthesia but before surgery; (3) 1 h after the start of the operation; (4) in the recovery room when the patient was fully awake. The plasma was separated within 30 min, frozen at −20 °C for storage and thawed within 1 month for radioimmunoassay for aldosterone by the method of Mayes and colleagues (1970) using 1.2-^{3}H-aldosterone (New England Nuclear Corporation) and antisera provided by Dr C. A. Nugent. The mean recovery rate for utilized 1.2-^{3}H-aldosterone by our method was 77% and the coefficient of variation (c.v.) was 6%.

Plasma renin activity was measured according to the method of Haber and colleagues (1969), using an angiotensin I radioimmunoassay kit utilizing ^{125}I-angiotensin I produced by CEA-IRE-SORIN Co. Ltd. Two millilitre of venous blood was mixed well in an iced test-tube which contained EDTA-2 Na 2 mg. The plasma was separated by frozen-centrifugation, and was kept at −20 °C for storage. The mean recovery rate was 72% and c.v. was 7%. The plasma concentrations of ACTH were determined by radioimmunoassay as described by Berson and Yalow (1968). The ^{125}I-ACTH kit was produced by Radiochemical Center Co. Ltd; the recovery rate was 40% and c.v. was 12%.

RESULTS

The plasma concentrations of aldosterone were increased markedly, being 2.5 times the control values during ether–nitrous oxide anaesthesia, 1.5 times during halothane–nitrous oxide or 1.6 times during methoxyflurane–nitrous oxide anaesthesia and two times during enflurane–nitrous oxide anaesthesia. There was a further increase to about three times greater than the control values at 0.5–2 h after the start of the surgery. Increased plasma concentrations of aldosterone were observed on the first day after operation (fig. 1). Spinal anaesthesia did not alter significantly the plasma concentrations of aldosterone or serum sodium or potassium.

The renin activity in the plasma was increased slightly during ether–nitrous oxide, halothane–nitrous oxide, enflurane–nitrous oxide anaesthesia and surgery (fig. 2). However, there were no significant changes in serum sodium or potassium concentrations in these groups. A significant decrease in urinary Na/K ratio with all the inhalation agents was

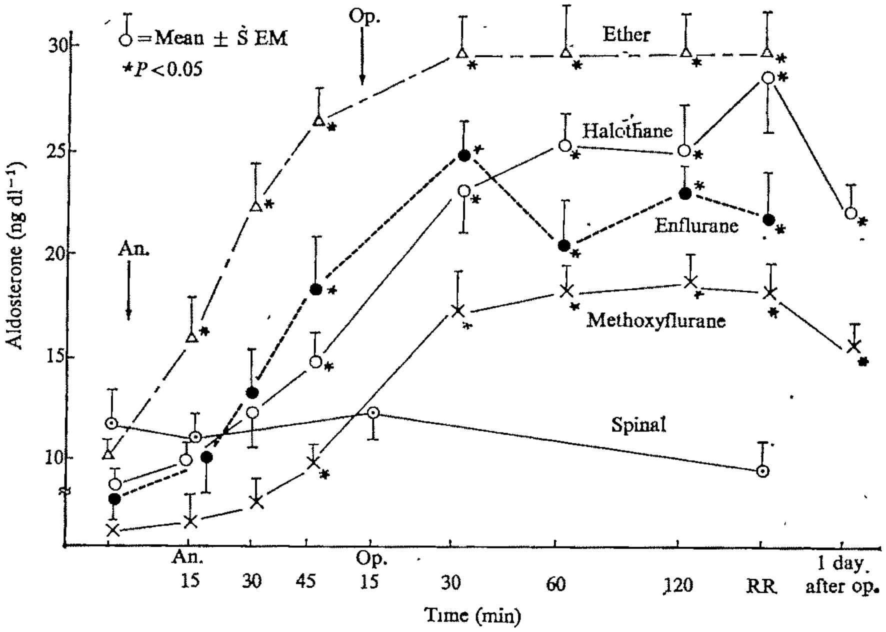

FIG. 1. Plasma aldosterone concentrations during and after anaesthesia and surgery. An. = anaesthesia; op. = operation; RR = recovery room.

associated with the increase in the plasma concentrations of aldosterone (fig. 3).

Although the plasma concentrations of ACTH increased slightly during halothane–nitrous oxide and enflurane–nitrous oxide anaesthesia, and were increased markedly during surgery, they had decreased by the 1st day after operation (fig. 4). The plasma concentrations of ACTH were not altered significantly during spinal anaesthesia, although they did increase slightly after surgery (fig. 4).

DISCUSSION

The renin–angiotensin–aldosterone system is important in the maintenance of the fluid and electrolyte

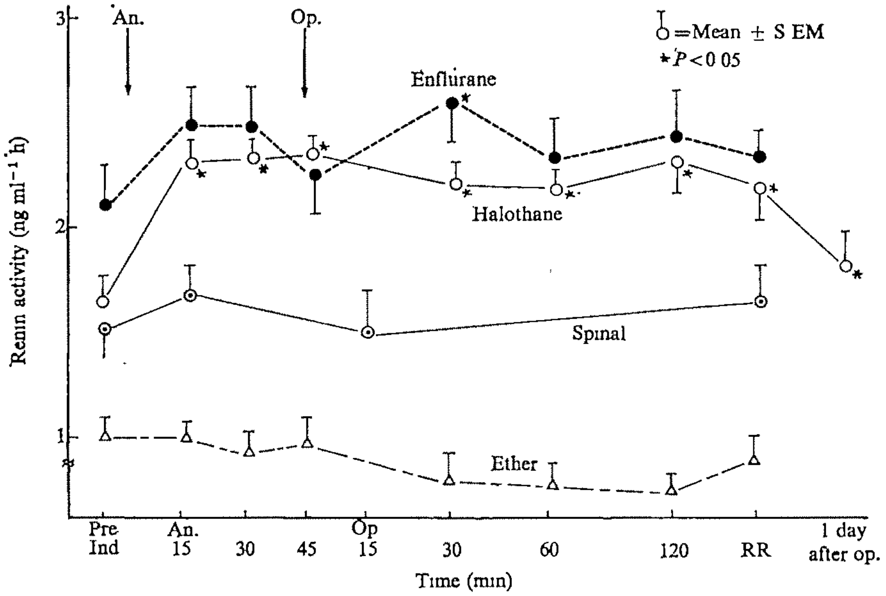

FIG. 2. Plasma renin activity during and after anaesthesia and surgery.

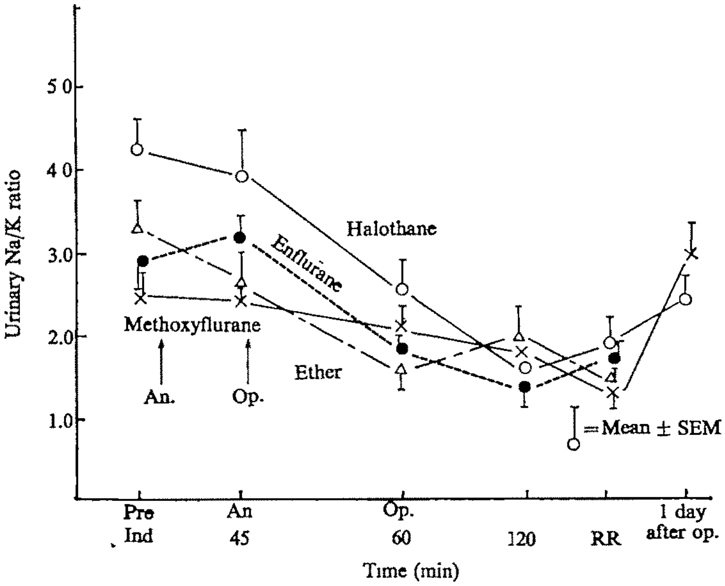

FIG. 3. Urinary Na/K ratio during and after anaesthesia and surgery.

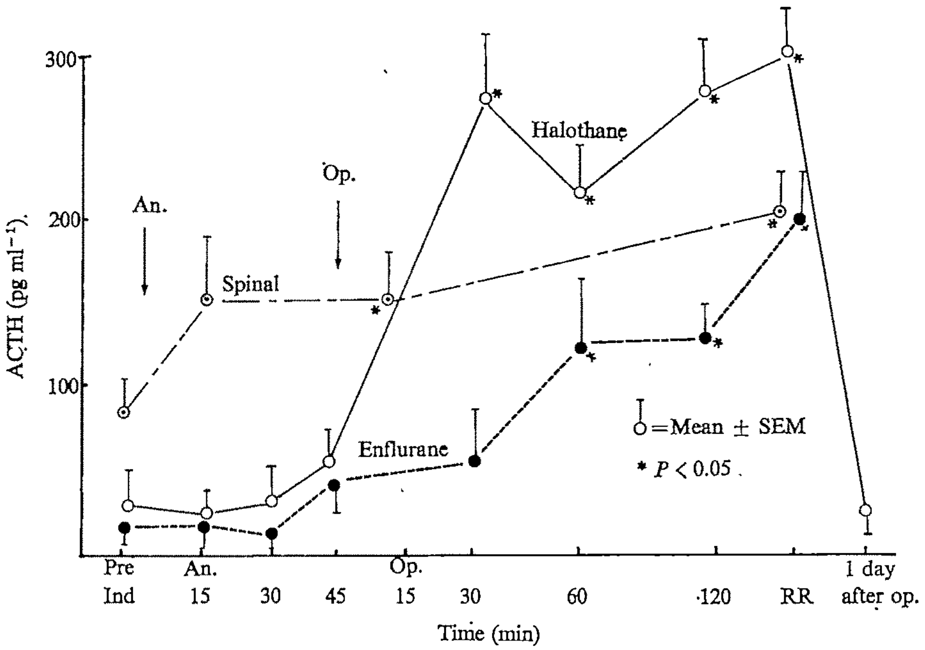

FIG. 4. Plasma ACTH concentration during and after anaesthesia and surgery.

balance and the arterial pressure. Aldosterone causes an increase in the tubular reabsorption of sodium and excretion of potassium, which decreases the urinary output of sodium and chloride but increases that of potassium, and thus expands the extracellular fluid compartment.

Plasma concentrations of aldosterone are influenced by many factors, such as its secretion from the zona glomerulosa of the adrenal cortex, metabolism in the liver, peripheral utilization, and renal excretion. However, the adrenal secretion appears to play the main role during stress. Hume, Bell and Bartter (1962) found that the secretion rate of aldosterone in the adrenal vein was increased after surgical stress. Aldosterone secretion is increased by ACTH, a decrease in the plasma concentration of sodium, an increase in potassium concentration, a decrease in the plasma sodium to potassium ratio and by a reduction in the extracellular fluid or blood volume.

A decrease in blood volume or in arterial pressure or vasoconstriction of the renal arteries decreases pressure in the afferent arteriole leading to a release of renin from the juxtaglomerular cells of the kidney. The renin converts angiotensinogen which is manufactured in the liver to angiotensin I. This substance is converted further in the blood stream by an enzyme to angiotensin II which stimulates the adrenal cortex to release aldosterone. As neither pregnant patients, nor any taking oral contraceptives, nor any suffering from the nephrotic sydrome were included in the study, the plasma renin activity represents plasma concentration of angiotensin. Aldosterone, in turn, leads to sodium retention and an increase in arterial pressure, which acts as a feedback mechanism to shut off the further release of renin.

It is not certain, however, whether this feedback mechanism operates during stress. In our present study the plasma renin activity did not increase significantly during anaesthesia, but it did increase significantly during surgery in man. According to Naruse (1970), plasma renin activity was not changed during the early part of the surgical procedure and increased only in the later part of the operation. Our findings accord with others which reported that neither halothane (Robertson and Michelakis, 1972) nor ketamine (Miller et al., 1975) caused any significant change in plasma renin activity. Therefore, the participation of the renin–angiotensin system in the increase in the concentrations of plasma aldosterone during anaesthesia appears to be minor. However, during surgery it may play a role.

The secretion of aldosterone is enhanced by the decreases in sodium and the increases in potassium concentrations. However, the variation in plasma electrolytes was small during anaesthesia and surgery. Therefore, it seems unlikely that changes in plasma electrolyte concentrations are a major regulatory mechanism during anaesthesia and surgery. According to Ganong (1973), in the dog the plasma potassium concentration must increase at least 1 mmol $litre^{-1}$ or the plasma sodium decrease by about 20 mmol $litre^{-1}$ before a stimulating effect is seen.

The authors' findings indicate that, although general anaesthesia with ether, halothane, methoxyflurane or enflurane stimulates the secretion of aldosterone from the adrenal cortex, spinal anaesthesia does not stimulate aldosterone secretion in man. The marked increase in ACTH secretion or the increased plasma renin activity, or both, appeared to play an important role in the increase in the concentration of aldosterone during the procedure. The magnitude of the surgical stress and the duration of spinal anaesthesia alone was less than those in the other inhalation anaesthetic groups. Therefore, it cannot be denied that this might contribute to the smaller response in aldosterone secretion in the spinal anaesthesia group.

An excess of aldosterone leads to an increase in extracellular fluid, sodium retention, potassium depletion and hypertension, while aldosterone deficiency leads to sodium depletion, potassium retention, hypovolaemia and hypotension. Therefore, aldosterone appears to play some role in homeostasis and serum electrolyte balance during anaesthesia and surgery (Miller, Ackerly and Peach, 1978).

Since there were no substantial differences in the plasma concentrations of aldosterone among the inhalation agents, any of these agents or techniques can be used for adrenalectomy in patients with primary hyperaldosteronism, except for methoxyflurane, which is nephrotoxic. From the theoretical point of view, spinal anaesthesia could become the anaesthetic of choice for these patients.

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EFFETS DE L'ANESTHESIE ET DE L'INTERVENTION CHIRURGICALE SUR LA CONCENTRATION D'ALDOSTERONE DANS LE PLASMA ET L'ACTIVITE DE LA RENINE CHEZ L'HOMME

RESUME

On a fait des recherches sur 76 malades en ce qui concerne les effets de divers agents anethésiants et des interventions chirurgicales sur les concentrations d'aldostérone dans le plasma et sur l'activité de la rénine. La concentration d'aldostérone dans le plasma a augmenté d'une manière importante, 2,5 fois les valeurs témoins, au cours d'une anesthésie à l'éther d'une durée de 45 min. Elle a également augmenté au cours d'anesthésies effectuées à l'halothane, au métoxyflurane et à l'enflurane. L'anesthésie rachidienne n'a pas modifié de manière significative la concentration d'aldostérone dans le plasma. La quantité de rénine et la concentration d'ACTH dans le plasma ont légèrement augmenté pendant l'anesthésie générale.

WIRKUNGEN VON ANÄSTHESIE UND OPERATIONEN AUF ALDOSTERON-PLASMAKONZENTRATIONEN UND RENIN-AKTIVITATEN BEI MENSCHEN

ZUSAMMENFASSUNG

Die Wirkungen verschiedener Anästhesiemittel und chirurgischer Eingriffe auf die Plasmakonzentrationen von Aldosteron und auf die Renin-Aktivität wurde bei 76 Patienten untersucht. Die Aldosteron-Konzentration stieg deutlich um 2,5 des Kontrollwertes, wahrend 45 Minuten einer Äthernarkose. Sie stieg auch bei Narkosen mit Halothan, Methoxyfluran und Enfluran. Ruckenmarksanästhesie veränderte die Aldosteron-Plasmakonzentration kaum. Die Plasma-Renin-Aktivität und die Aldosteron-Konzentration stiegen leicht während einer allgemeinen Narkose.

EFECTOS EJERCIDOS POR ANESTESIA Y CIRUJIA SOBRE LA CONCENTRACION DE ALDOSTERONA Y LA ACTIVIDAD DE RENINA EN LA PLASMA DEL HOMBRE

SUMARIO

Se investigaron los efectos ejercidos por diversos agentes anestésicos y cirujía sobre las concentraciones de aldosterona en la plasma y sobre la actividad de renina en 76 pacientes. La concentración de aldosterona en la plasma aumentó notablemente a un valor 2,5 veces superior al de control durante 45 min de anestesia con éter. Aumentó también durante la anestesia de halotano, metoxiflurano y enflurano. La anestesia espinal no alteró significativamente la concentración de aldosterona en la plasma. La actividad de renina en la plasma y la concentración de ACTH aumentaron ligeramente durante anestesia general.

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A SCREENING TEST FOR THE MALIGNANT HYPERPYREXIA PHENOTYPE USING SUXAMETHONIUM-INDUCED CONTRACTURE OF MUSCLE TREATED WITH CAFFEINE, AND ITS INHIBITION BY DANTROLENE

P. J. HALSALL AND F. R. ELLIS

SUMMARY

Suxamethonium induced a contracture in caffeine pretreated human muscle *in vitro*. The contracture was significantly greater ($P < 0.001$) with MHS muscle compared with muscle from normal subjects. This reaction is now used as an additional screening test for the MHS phenotype. The contracture was prevented by pretreatment with dantrolene.

The diagnosis of susceptibility to malignant hyperpyrexia (MHS) depends on the demonstration of halothane-induced contracture of a muscle biopsy specimen at 37 °C *in vitro* (Ellis et al., 1978). Although the diagnosis of MHS is made in our laboratory from the results of the halothane contracture test, the caffeine and caffeine/halothane sensitivities of the muscle are determined routinely in a manner similar to that described by Kalow, Britt and Richter (1977), with the modification that all investigations are made at 37 °C. Moulds and Denborough (1974) used potassium chloride and suxamethonium, in addition to halothane and caffeine, to induce contracture of MHS muscle. We have rarely obtained significant contractures of MHS muscle with suxamethonium alone. However, Moulds (personal communication) described a method combining caffeine and suxamethonium which induces a contracture in normal muscle. It was decided to study this combination as a possible additional method of screening MHS patients.

The effect of dantrolene on the contracture produced by this drug combination was studied in view of its potential importance in the treatment of the patient developing MH and the associated muscle contracture.

METHODS

Twenty consecutive patients being screened for MH were studied. All were apparently healthy, aged 12–45 yr. The muscle biopsy was taken across the motor point in the left vastus medialis muscle under general anaesthesia (Cain and Ellis, 1977). The biopsy specimens were placed in fresh oxygenated Krebs solution and transported to the laboratory at room temperature. Fresh muscle fibres measuring 20 mm × 2 mm × 1 mm were dissected from the gross biopsy specimens and placed in a 2-ml tissue bath and perfused with fresh oxygenated Krebs solution at 37 °C. The apparatus and technique used were those described by Ellis and others (1978). The muscle was stretched to a tension of 2 g measured from an isometric strain gauge (Devices 662 100), recording on a Devices M2 recorder. Each specimen was stimulated at a rate of 0.5 Hz using a DS9 Digitimeter Stimulator to ensure viability.

After allowing for the isometric relaxation which normally follows muscle stretching, the muscle was perfused with caffeine 4 mmol at a constant rate until a maximum contracture had occurred, or until 3–4 min had elapsed in the absence of a contracture. Suxamethonium was added to the tissue bath to give a concentration of 6.29 mmol and the contracture produced by the muscle was recorded. The addition of suxamethonium was repeated after 1 min. Finally, the muscle specimen was removed and weighed. Only one specimen from each patient was tested.

A fresh sample was placed in the tissue bath and after stretching to a tension of 2 g it was perfused with dantrolene in concentrations of either 0.04 or 0.08 mmol litre^{-1} in Krebs solution. The dantrolene solution was prepared as described by Harrison (1975). Suxamethonium was added to the tissue bath following the same procedure as before and the contracture produced by the muscle was recorded.

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Statistical evaluation of the results was made using Student's t test for unpaired means and differences between the means were assessed using two-tailed probability distribution tables.

RESULTS

Of the 20 patients studied, 10 were found to be MHS and 10 were normal (MHN) according to the results of the halothane challenge test.

TABLE I. *Mean changes in tension (g) ± SEM developed by muscle samples after administration of suxamethonium 6.29 mmol litre⁻¹ with tissue bath perfused with Krebs solution containing caffeine 4 mmol litre⁻¹*

	Tension (g)		Significance between MHS and MHN groups	
	MHS	MHN	t	P
1st exposure	4.8 ± 0.82	0.1 ± 0.06	5.76	< 0.001
2nd exposure	5.72 ± 0.84	0.34 ± 0.1	6.31	< 0.001

From table I it can be seen that the muscle contractures induced by the suxamethonium/caffeine combination in a perfused tissue bath were significantly greater in the MHS group compared with the MHN group. Typical tracings produced by caffeine and suxamethonium are shown in figures 1A (MHS) and 2A (MHN). From these tracings it may be seen that the response produced by MHS muscle occurred rapidly, whereas that produced by MHN muscle occurred slowly, if at all. There was no significant difference between the weights of muscle samples in the two groups ($P > 0.9$).

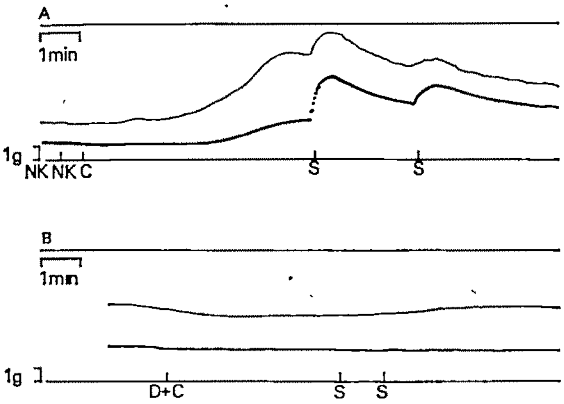

FIG. 1. A: Trace showing the contracture produced by caffeinated MHS muscle with the administration of suxamethonium 6.29 mmol litre⁻¹. The thick base line indicates muscle tension and the thin upper line the muscle twitch height. C = caffeine 4 mmol litre⁻¹; S = suxamethonium 6.29 mmol litre⁻¹; NK = Krebs solution. B: Trace showing the effect of dantrolene 0.04 mmol litre⁻¹ on the contracture produced by MHS muscle with caffeine 4 mmol litre⁻¹ and suxamethonium 6.29 mmol litre⁻¹. D = dantrolene 0.04 mmol litre⁻¹.

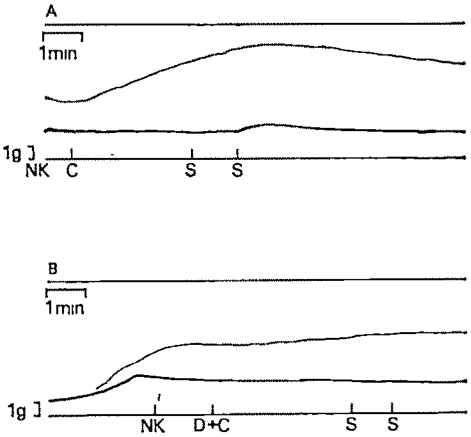

FIG. 2. A: Trace showing the effect of suxamethonium 6.29 mmol litre⁻¹ on normal caffeinated muscle. B: Trace showing the effect of dantrolene 0.04 mmol litre⁻¹ on the contracture produced by normal muscle with suxamethonium 6.29 mmol litre⁻¹ and caffeine 4 mmol litre⁻¹.

The results of the effect of dantrolene on muscle contracture induced by caffeine/suxamethonium are shown in table II. Dantrolene 0.04 mmol litre⁻¹ was effective in preventing the induced contractures in most muscle samples from both MHS and MHN patients. A statistical evaluation of these findings is

TABLE II. *Mean changes in tension (g) developed by muscle samples after administration of suxamethonium 6.29 mmol litre⁻¹ with perfusion of Krebs solution containing dantrolene and caffeine*

	Tension (g)	
	MHS	MHN
1st exposure	0.16 ± 0.1	0 ± 0
2nd exposure	0.48 ± 0.2	0.02 ± 0.02

TABLE III. *Tests of significance between tables I and II for MHS and MHN groups*

	MHS comparison		MHN comparison	
	t	P	t	P
1st exposure	5.34	< 0.001	1.63	n.s.
2nd exposure	5.59	< 0.001	4.05	< 0.001

shown in table III. Figures 1B (MHS) and 2B (MHN) show the typical response to caffeine/suxamethonium after pretreatment with dantrolene. In the three muscle samples most sensitive to the combination of caffeine and suxamethonium, dantrolene 0.04 mmol litre^{-1} was insufficient to prevent a contracture occurring, although the contracture height was reduced. In two of these samples the concentration of dantrolene was increased to 0.08 mmol litre. This greater concentration further reduced the contracture height, but did not prevent its occurrence. The difference between the weights of muscle samples in the MHS and MHN treated and untreated groups was not statistically significant ($P > 0.4$).

DISCUSSION

Normal muscle responds to caffeine by producing a gradual increase in tension as a result of both the release of Ca^{2+} from storage sites in the sarcoplasmic reticulum (SR) and by preventing re-accumulation of Ca^{2+} by the SR which allows relaxation (Bianchi, 1963; Herz and Weber, 1965). Suxamethonium alone never produces any change in tension in normal muscle *in vitro*. In our experience, only in two patients from one family has suxamethonium alone ever produced a contracture of MHS muscle *in vitro*. Thus, the contracture induced by the caffeine/suxamethonium combination must be a synergistic action. Since suxamethonium is a large, charged molecule which does not cross a charged cell membrane, it is reasonable to suppose that it is acting at the cell membrane rather than in the cell itself. It may be that small increases in movement of "trigger" Ca^{2+} across the cell membrane with suxamethonium (the first part of excitation–contraction coupling), have an explosive effect on the intracellular Ca^{2+} translocations in the sarcoplasmic reticulum already stimulated by caffeine (the second part of excitation–contraction coupling). Hence the immediate dramatic increase in tension seen after the drug combination (fig. 1).

The prevention by dantrolene of the caffeine/suxamethonium contracture suggests that a least two of these drugs act at the same site in the excitation–contraction coupling system. Dantrolene may uncouple this system by its effects on calcium mobilization either at the plasma membrane site or in the sarcoplasmic reticulum (Ellis and Bryant, 1972; Nelson, 1978).

The synergistic interaction of caffeine and suxamethonium distinguishes between MHS and MHN muscle. Unlike the halothane contracture test, the caffeine/suxamethonium test produces a graded response and is a useful additional test when investigating a patient's susceptibility to MH. The result of the halothane contracture test still remains the main diagnostic criterion.

It is hoped to use the new test to help to distinguish between the possibly various MHS phenotypes suggested by Kalow, Britt and Richter (1977) and Ellis and others (1978).

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ESSAI DE DEPISTAGE DU PHENOTYPE D'HYPERPYREXIE MALIGNE A L'AIDE DE LA CONTRACTURE DU MUSCLE TRAITE A LA CAFEINE, PROVOQUEE PAR LE SUXAMETHONIUM DE MEME QUE SON INHIBITION PAR LE DANTROLENE

RESUME

Le suxaméthonium a provoqué *in vitro* la contracture d'un muscle humain prétraité à la caféine. La contracture a été beaucoup plus forte ($P < 0{,}001$) avec les muscles réagissant à l'hyperpyrexie maligne qu'avec les muscles des sujets normaux. On se sert maintenant de cette réaction comme essai de dépistage supplémentaire pour le phénotype d'hyperpyrexie maligne. La contracture a été empêchée par un prétraitement au dantrolène.

EIN AUSWAHLVERSUCH FÜR DEN PHÄNOTYP DER MALIGNEN HYPERPYREXIE UNTER VERWENDUNG EINER DURCH SUXAMETHONIUM BEWIRKTEN MUSKELZUSAMMENZIEHUNG, BEHANDELT MIT KOFFEIN, UND IHRE UNTERDRÜCKUNG DURCH DANTROLEN

ZUSAMMENFASSUNG

Suxamethonium bewirkte *in vitro* die Zusammenziehung eines mit Koffein vorbehandelten menschlichen Muskels. Die Kontraktur war wesentlich grosser ($P < 0,001$) beif auf maligne Hyperpyrexie anfalligen Muskeln, als bei Muskeln gesunder Personen. Diese Reaktion wird nun als zusätzlicher Test für den Phanotype der Anfälligkeit auf maligne Hyperpyrexie verwendet. Die Kontraktur wurde durch Vorbehandlung mit Dantrolen verhindert.

UNA PRUEBA DE SELECCION EN BUSCA DEL FENOTIPO HIPERPIREXIA MALIGNA, UTILIZANDO LA CONTRACTURA MUSCULAR INDUCIDA POR SUXAMETONIO, TRATADA CON CAFEINA Y SU INHIBICION CON DANTROLINA

SUMARIO

El suxametonio indujo una contractura en el músculo humano pretratado con cafeína *en vitro*. La contractura fue significativamente mayor ($P < 0,001$) en el músculo susceptible a hiperpirexia maligna, en comparación con el músculo de sujetos normales. Esta reacción es ahora empleada como una prueba de selección adicional para descubrir el fenotipo hiperpirexia maligna. La contractura fue evitada mediante pretratamiento con dantrolina.

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I.C.P. INCREASES WITH 50% NITROUS OXIDE IN OXYGEN IN SEVERE HEAD INJURIES DURING CONTROLLED VENTILATION

E. MOSS AND D. G. McDOWALL

SUMMARY

In a randomized trial nitrous oxide 50% in oxygen (Entonox) or oxygen 100% was given during chest physiotherapy on 23 occasions to three mechanically ventilated patients with severe head injuries. Intracranial pressure (i.c.p.) increased by 22.7 mm Hg (SD 10.62) during chest physiotherapy with Entonox, compared with 10.5 mm Hg (SD 10.4) with oxygen 100% ($P > 0.02$). A further nine mechanically ventilated patients with severe head injuries were given Entonox without chest physiotherapy. There was a mean increase in i.c.p. of 3.8 mm Hg (SD 2.4) ($P < 0.001$) when Entonox was given, and a mean decrease of 4.6 mm Hg (SD 2.8) when the nitrous oxide was withdrawn. End-tidal carbon dioxide concentration showed almost no change during nitrous oxide administration (decrease of 0–0.1%). We conclude that nitrous oxide causes an increase in i.c.p. in patients with severe head injuries and exacerbates the increases in i.c.p. occurring during chest physiotherapy.

Nitrous oxide is used widely in intensive care units as a 50% mixture with oxygen (Entonox) to produce analgesia during chest physiotherapy and other painful procedures. The aim of this study was to determine whether the administration of nitrous oxide 50% in oxygen would prevent or decrease the increases in intracranial pressure (i.c.p.) which occur normally during chest physiotherapy in patients with severe head injuries (Gibson et al., 1975). The results obtained prompted a second investigation into the effects of nitrous oxide in oxygen on i.c.p. in the absence of chest physiotherapy.

METHODS

The changes in i.c.p. which occurred during chest physiotherapy were compared during administration of either oxygen 100% or nitrous oxide 50% in oxygen (Entonox).

Random number tables were used to determine the treatment for each episode of chest physiotherapy. There were three patients in the trial, all of whom had severe head injury and whose lungs were being ventilated mechanically. During chest physiotherapy the lungs were "bagged" by an anaesthetist, using a Mapleson C system (Mapleson, 1954) (fresh gas flow of greater than twice the minute volume of the patient). I.c.p. was recorded continuously from a subdural catheter or device, or an extradural device (Coroneos et al., 1973) connected to a transducer, the signal from which was amplified and recorded on a Devices chart recorder. The maximum increase in mean i.c.p. occurring during the period of chest physiotherapy was obtained from the chart recordings. This trial was terminated prematurely when it was found that the administration of Entonox was accentuating the changes in i.c.p. produced by chest physiotherapy.

In a second study, the effect of Entonox on i.c.p. was studied in a further nine patients with severe head injury during mechanical ventilation. However, in these patients physiotherapy was not undertaken. In these patients IPPV had been established for at least 6 h with Pa_{CO_2} values between 3.3 and 4.0 kPa. No patient was included who required an inspired oxygen concentration greater than 50%. I.c.p. was measured as described above, and was recorded at a fast chart speed for 10 min before the administration of Entonox, for either 5 min (two administrations) or 10 min (14 administrations) during the administration of Entonox (through the oxygen inlet of the Cape ventilator), and for 10 min after the discontinuation of the Entonox. During the last six administrations of Entonox, end-tidal carbon dioxide concentration was measured by mass spectrometry (Medishield). Arterial blood-gas tensions were measured within 4 h of the administration of the Entonox as part of the routine management of the patient in the intensive care ward.

RESULTS

Mean i.c.p. before chest physiotherapy was the same in the 100% oxygen group as in the Entonox group.

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I.c.p. increased by 22.7 mm Hg (SD 10.6) when physiotherapy was performed with Entonox compared with 10.5 mm Hg (SD 10.4) during the administration of oxygen ($0.02 > P > 0.01$) (table I and fig. 1). In two patients A-waves (Lundberg, 1960) were precipitated by Entonox and physiotherapy, but this occurred also in one patient when physiotherapy was being carried out with oxygen alone.

TABLE I. *Comparison of increases in i.c.p. produced by chest physiotherapy during* 100% *oxygen and during Entonox administration. Control values are those of mean i.c.p. before physiotherapy.* *$0.02 > P > 0.01$

	Oxygen		Entonox	
	Control (mm Hg)	Change from control (mm Hg)	Control (mm Hg)	Change from control (mm Hg)
	7	+10	19	+16
	15	+40	15	+40
	26	+15	16	+40
	18	+3	7	+6
	9	+4	10	+11
	13	+4	8	+23
	14	+10	10	+23
	7	+5	12	+19
	13	+9	10	+22
	9	+7	13	+33
	10	+8	12	+15
			14	+24
n	11		12	
$\bar{x}$	12.8	+10.5*	12.2	+22.7*
SD	5.6	10.4	3.5	10.6

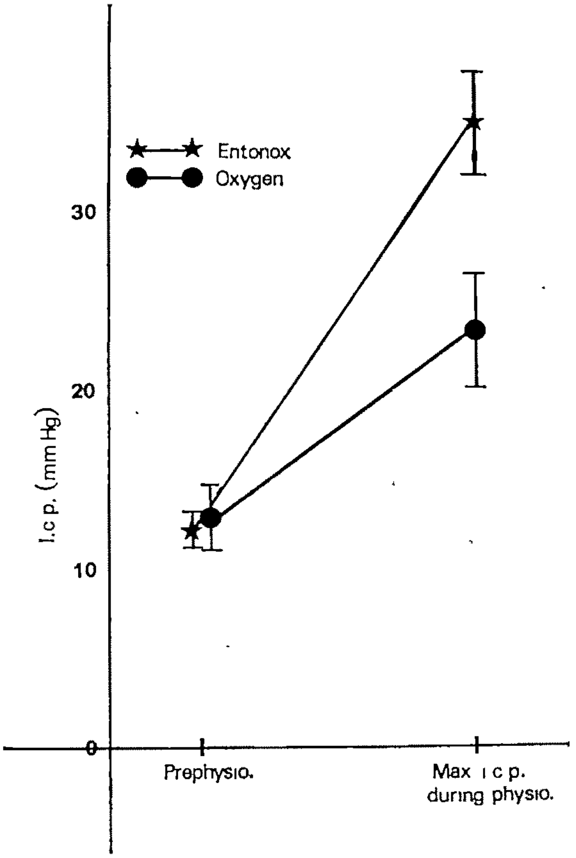

FIG. 1. Comparison of the increases in i.c.p. with chest physiotherapy during Entonox and 100% oxygen administration in patients with severe head injuries. The bars represent the standard errors of the means.

When Entonox was administered to patients not undergoing chest physiotherapy there was a mean increase in i.c.p. of 3.8. mm Hg (SD 2.4) (range 0–8.5 mm Hg) ($P < 0.001$). After the withdrawal of nitrous oxide there was a mean decrease in i.c.p. of 4.6 mm Hg (SD 2.8) ($P < 0.001$) (table II and fig. 2).

There was a mean decrease in end-tidal carbon dioxide concentration of less than 0.1% (range 0–0.1%) when nitrous oxide was given.

DISCUSSION

Reports on the effect of nitrous oxide on i.c.p. are contradictory. In dogs, Saidman and Eger (1965) showed no change in i.c.p. with 70–75% nitrous oxide, whereas Sakabe and colleagues (1978) found an increase in i.c.p. In man, increases in i.c.p. have been reported during the induction of anaesthesia in patients with intracranial tumours and aneurysms (Sondergard, 1961; Hulme and Cooper, 1972; Henriksen and Jorgensen, 1973; Greenbaum et al., 1975; Phirman and Shapiro, 1977), and during established anaesthesia with hypocapnia in patients with cerebral tumours (Misfeldt, Jörgensen and Rishöj, 1974). However, Gordon and Greitz (1970) found no increase in lumbar cerebrospinal fluid pressure when nitrous oxide was administered with the anaesthetic gases to patients with normal i.c.p.

Increases in cerebral blood flow (c.b.f.) occur on the administration of nitrous oxide to dogs (McDowall and Harper, 1965; Theye and Michenfelder, 1968; Sakabe et al., 1978), but the reports in man are conflicting. Wollman and others (1965) reported no change in c.b.f. when 70% nitrous oxide was given to healthy male volunteers, whereas Sakabe and others (1976) found an increase in c.b.f. with 60% nitrous oxide in human volunteers. There has been no report

TABLE II. *I.c.p. (mm Hg) before, during and after Entonox. The peak values reached during Entonox administration were used in calculating the changes*

Patient	Control	Change after N_2O administration	Change after N_2O withdrawal
A	4	+1	−2
	13	+5	−1
	6.5	+4.5	−5
B	13.5	+2	−3.5
C	6	+1	−1
D	16	+2	−4
E	3	+7	−4
	3	+2	−4
	1	+6	−6
F	22	+4	−11
G	1	+6	−6
	6	+5	−8
H	5	0	−0.5
I	25.5	+8.5	−8
	21	+3	−5
	23	+3	−5
$(n = 16)$			
$\bar{x}$	10.6	$d = +3.8$	$d = -4.6$
SD	8.53	2.40	2.83
		$P < 0.001$	$P < 0.001$

of the effect of nitrous oxide on i.c.p. or c.b.f. in patients with severe head injury, although it has been suggested that increases may occur (Henriksen and Jorgensen, 1973).

Gibson and co-workers (1975) reported increases in i.c.p. during chest physiotherapy in patients with severe head injuries, which were thought to be partly a result of systemic hypertension and partly a result of cerebral activation produced by noxious stimulation. As Entonox is an analgesic, it might be expected to decrease such increases in i.c.p. However, after Entonox had been given on 12 occasions during chest physiotherapy, it was clear that the increases in i.c.p. were exacerbated.

The increase in i.c.p. with Entonox in the absence of chest physiotherapy is almost certainly a result of a cerebral vasodilatory action of the drug. An increase in end-tidal carbon dioxide concentration, which was expected because of the initial rapid uptake of nitrous oxide, was not seen and therefore cannot account for the increase in i.c.p. The increases in i.c.p. recorded here, in the absence of chest physiotherapy, were small but might be greater in patients with severe head injury breathing spontaneously, especially when the volume of the intracranial contents is on the steep part of the pressure–volume curve.

The use of nitrous oxide for general anaesthesia in head injuries is not contraindicated by our results, but

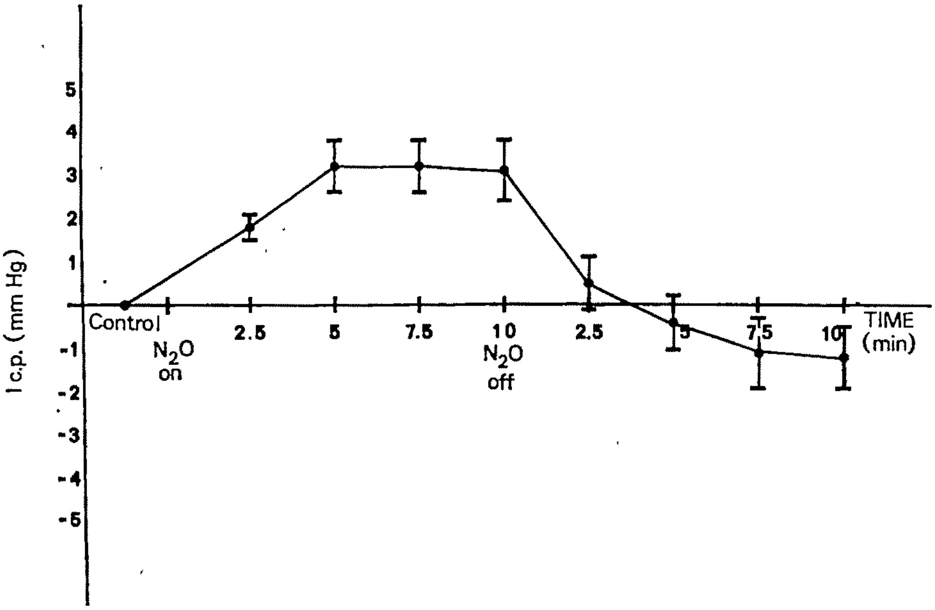

FIG. 2. The effect of Entonox on i.c.p. in nine patients with severe head injuries. The control value represents the mean i.c.p. in the 10 min before administration of Entonox. The bars represent the standard errors of the means.

hypocapnia should probably be induced first by hyperventilation with oxygen 100%.

Misfeldt and colleagues (1974) showed that prior hyperventilation for 10 min or more with oxygen 100% prevented any marked increase in i.c.p. during the administration of nitrous oxide. However, when controlled hyperventilation has been in use for some hours, as in the management of severe head injury, any protective effect of hypocapnia against the increases in i.c.p. induced by nitrous oxide may be lost because of the adaptation of c.b.f. and i.c.p. with time to the low Pa_{CO_2} values.

Finally, the results obtained here suggest that Entonox should be avoided in spontaneously-breathing head-injured patients during transport and admission to hospital.

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AUGMENTATIONS DE LA PRESSION INTRA-CRANIENNE AVEC 50% DE PROTOXYDE D'AZOTE DANS L'OXYGENE DANS LES CAS DE BLESSURES GRAVES A LA TETE PENDANT UNE VENTILATION CONTROLEE

RESUME

Au cours d'essais effectués au hasard, on a administré soit 50% de protoxyde d'azote dans l'oxygène (Entonox), soit 100% d'oxygène pendant une physiothérapie de la poitrine et ce à 23 reprises à trois patients ventilés mécaniquement et souffrant de blessures graves à la tête. La pression intracranienne (i.c.p.) a augmenté de 22,5 mm Hg (écart type 10,62) pendant la physiothérapie de la poitrine à l'aide d'Entonox, par rapport à 10,5 mm Hg (écart type 10,4) lorsqu'on a utilisé de l'oxygène à 100% ($P > 0{,}02$). Neuf autres malades ventilés mécaniquement et souffrant également de blessures graves à la tête se sont vus administrer de l'Entonox sans physiothérapie de la poitrine. Il s'est produit une augmentation moyenne de l'i.c.p. de 3,8 mm Hg (écart type 2,4) ($P < 0{,}001$) lorsque l'Entonox a été administré et une diminution moyenne de 4,6 mm Hg (écart type 2,8) lorsque le protoxyde d'azote a été arrêté. La concentration d'acide carbonique en fin d'expiration n'a virtuellement accusé aucun changement pendant l'administration de protoxyde d'azote (diminution de 0–0, 1%). Nous en concluons que le protoxyde d'azote provoque une augmentation de l'i.c.p. chez les malades souffrant de blessures graves à la tête et aggrave l'augmentation de l'i.c.p. qui se produit pendant la physiothérapie de la poitrine.

INTRAKRANIELLER DRUCK (I.C.P.) STEIG BEI KONTROLLIERTER BELÜFTUNG VON PATIENTEN MIT SCHWEREN KOPFVERLETZUNGEN BEI VERABREICHUNG VON 50% STICKOXYD IN SAUERSTOFF

ZUSAMMENFASSUNG

Bei einem wahllos durchgeführten Versuch wurden 50% Stickoxyd in Sauerstoff (Entonox) oder 100% Sauerstoff bei 23 Gelegenheiten wahrend Brust-Physiotherapie an drei mechanisch beluftete Patienten mit schweren Kopfverletzungen verabreicht. I.c.p. stieg um 22,7 mm Hg (SD 10,62) wahrend der Brust-Physiotherapie mit Entonox, verglichen mit 10,5 mm Hg (SD 10,4) mit 100% Sauerstoff ($P < 0,02$). Weiter neun mechanisch belüftete Patienten mit schweren Kopfverletzungen erhielten Entonox ohne Brust-Physiotherapie. Es kam zu einem mittleren Anstieg von i.c.p. von 3,8 mm Hg (SD 2,4) ($P < 0,001$), wenn Entonox verabreicht wurde, und zu einem mittleren Abstieg von 4,6 mm Hg (SD 2,8) bei Entzug von Stickoxyd. Die Endausatmungskonzentration von Kohlendioxyd zeigte fast keine Veränderung während der Verabreichung von Stickoxyd (Abstieg von 0–0,1%). Wir schliessen daraus, dass Stickoxyd einen Anstieg von i.c.p. bei Patienten mit schweren Kopfverletzungen bewirkt, und den Anstieg von i.c.p., zu dem es wahrend Brust-Physiotherapie kommt, verschlechtert.

AUMENTOS EN LA PRESION INTRACRANEAL CON 50% DE OXIDO NITROSO EN OXIGENO PARA SERIAS LESIONES A LA CABEZA DURANTE VENTILACION CONTROLADA

SUMARIO

En una prueba aleatoria, se administró óxido nitroso 50% en oxígeno (Entonox) u oxígeno 100% durante la fisioterapia del pecho, en 23 ocasiones, a tres pacientes ventilados mecánicamente que habían sufrido serias lesiones a la cabeza. La presión intracraneal (p.i.c.) aumentó en un 22,7 mm Hg (SD 10,62) durante la fisioterapia del pecho con Entronox, en comparación con 10,5 mm Hg (SD 10,4) con oxígeno 100% ($P < 0,02$). Otros nueve pacientes mecánicamente ventilados con lesiones severas a la cabeza recibieron Entonox sin fisioterapia del pecho. Se produjo una p.i.c. media de 3,8 mm Hg (SD 2,4) ($P < 0,001$) cuando se administró Entonox, y una disminución media de 4,6 mm Hg (SD 2,8) cuando se suspendió la administración de óxido nitroso. La concentración de dióxido de carbono al fin mareal prácticamente no acusó cambio alguno durante la administración de óxido nitroso (disminución de 0–0,1%). Concluímos que el óxido nitroso produce un aumento en la p.i.c. en aquellos pacientes con serias lesiones a la cabeza y exacerba los aumentos de p.i.c. que se producen durante la fisioterapia del pecho.

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HALOTHANE HEPATITIS REVISITED IN WOMEN UNDERGOING TREATMENT OF CARCINOMA OF THE CERVIX

H. J. WARK, B. CLIFTON AND M. J. BOOKALLIL

SUMMARY

From 1964 to 1976, 238 patients with carcinoma of the cervix were treated with irradiation and surgery. Their medical records were reviewed retrospectively. Three patients became jaundiced after operation as a result of pigment overload and sepsis. Exposure to halothane did not appear to be a significant aetiological factor.

A relationship between jaundice after operation, repeated halothane anaesthesia and irradiation of carcinoma of the cervix has been postulated (Ashton, O'Connor and Williams, 1963). Pratilas and Pratila (1976) suggested that halothane be avoided in these circumstances. On the other hand, Samrah (1963) reported more than 400 triple exposures to halothane during irradiation of the cervix without a single instance of jaundice or hepatic necrosis. These conflicting opinions about this possible relationship prompted us to review our experience at the Royal Prince Alfred Hospital, Sydney.

METHODS

The case records of all patients admitted between 1964 and 1976 with a diagnosis of carcinoma of the cervix were reviewed. Any mention of liver dysfunction or jaundice after operation was recorded.

From the anaesthetic records we obtained the dates of operative procedures and the anaesthetic agents employed.

RESULTS

Of the 238 patients treated for carcinoma of the cervix, 199 had radium inserted into the cervix under nitrous oxide, oxygen and halothane anaesthesia. One hundred and nineteen patients received at least one further halothane anaesthetic within a 6-week period. Three patients became jaundiced after operation (table I).

Patient 1

In 1965 a 36-yr-old woman had a subtotal hysterectomy for fibroids (first anaesthetic). On April 30, 1970, radium was inserted to the cervix to treat a stage-two carcinoma of the residual cervix (second anaesthetic).

The patient developed subacute small bowel obstruction and had a laparotomy and division of adhesions on June 13 (third anaesthetic). After this operation she developed a recto-vaginal fistula. Cystoscopy and examination under anaesthesia on August 6 (fourth anaesthetic) was followed on August 13 by a posterior exenteration and colostomy (fifth anaesthetic). All five anaesthetics included halothane. After the extenteration the patient again developed intestinal obstruction and at an operation on August 28, an ileal loop was adherent to a haematoma in the pelvic cavity. This loop was resected and a primary anastomosis performed.

Halothane was not used at this operation (sixth anaesthetic). On August 31, the patient was jaundiced and had bile in the urine. Serum bilirubin concentration was 135 i.u. litre^{-1} (normal 5–18 i.u. litre^{-1}), serum alkaline phosphatase 70 i.u. litre^{-1} (normal 35–90 i.u. litre^{-1}), and serum aspartate aminotransferase 60 i.u. litre^{-1} (normal 25–60 i.u. litre^{-1}). Four days after ileal resection a faecal fistula developed, and on September 3, laparotomy was performed (seventh anaesthetic). At operation it was found that the ileal anastomosis had broken down. The ileum was reanastomosed and a defunctioning ileostomy performed. Halothane was used at this operation although the serum bilirubin was still greater than 130 i.u. litre^{-1}. After this operation the jaundice gradually disappeared and on September 24 serum bilirubin was 18 i.u. litre^{-1}. The patient died

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TABLE I. *Summary of the clinical data*

Halothane anaesthetics	Number of patients	Jaundice	Max. serum bilirubin (μmol litre^{-1})	Max. alk. phosphatase (i.u. litre^{-1})	Max. aspart. transferase (i.u. litre^{-1})	
At least two in 6 weeks	119	2	135	70	60	Pigment overload infected haematoma
			61	181	38	Septicaemia, pneumonia, severe dehydration, hypotension
One or none	118	0	—	—	—	—
Uncertain	1	1	135	44	14	Pigment overload

on September 30, from generalized abdominal sepsis; no postmortem was performed.

Patient 2

In October 1972, a 72-yr-old woman underwent uterine curettage for menorrhagia at another hospital. A record of the anaesthetic was not available. Histological examination showed carcinoma of the cervix. On November 7, the patient's temperature was 39 °C, haemoglobin concentration 9.3 g dl^{-1} and she had lower abdominal pain and tenderness. Pyometra was suspected, and antibiotic therapy was commenced.

On November 25, 2 units of concentrated red cells were given for the treatment of anaemia. On December 8, Wertheim's panhysterectomy was performed, and a large left tubo-ovarian abscess drained. Halothane was not used in this operation. Several doses of prochlorperazine were given, on December 9, for nausea following surgery. Two days after operation the patient was jaundiced and with bilirubinuria. Serum bilirubin concentration was 135 i.u. litre^{-1}, serum alkaline phosphatase 44 i.u. litre^{-1}, serum aspartate aminotransferase 16 i.u. litre^{-1} and serum lactate dehydrogenase 240 i.u. litre^{-1} (normal 130–300 i.u. litre^{-1}). Schumm's test was negative and the serum haptoglobin concentration was normal. Ten days after operation the bilirubin had decreased to 15 i.u. litre–^{1}.

Patient 3

A 62-yr-old woman had radium inserted into the cervix on March 3, 1975, to treat a stage-two carcinoma of the cervix. Halothane was used during this anaesthetic.

On April 24, the patient was anaesthetized with halothane (amongst other agents) for Wertheim's hysterectomy. At laparotomy metastases in the liver were found and, after liver biopsy, the abdomen was closed. On May 20, while receiving a course of external cobalt irradiation, the patient developed pneumonia and septicaemia; jaundice was noted (serum bilirubin 51 i.u. litre^{-1}, serum alkaline phosphatase 181 i.u. litre^{-1}, serum aspartate aminotransferase 38 i.u. litre^{-1}). On June 8 the patient's serum bilirubin concentration had decreased to 20 i.u. litre^{-1}.

DISCUSSION

Ashton, O'Connor and Williams (1963) reported three cases of hepato-cellular liver failure in a 2-year study of patients with carcinoma of either the cervix or the body of the uterus. All three patients had multiple exposure to halothane over a short period of time. These authors questioned if "the combination of radium and halothane is rather more likely to cause liver damage than the administration of halothane alone".

Hughes (1967) and Hughes and Powell (1970) reported six cases of jaundice with two deaths in a two-and-a-half-year study of patients exposed to two or more halothane anaesthetics for radium treatment of carcinoma of the cervix. Davis and Holdsworth (1973) reported three cases of jaundice in patients who had had more than one halothane anaesthetic for treatment which included radium insertion. This occurred in a group which could not have contained more than 57 possible cases of carcinoma of the body or cervix of the uterus.

In all these case reports of jaundice, an alternative cause of the liver failure could be postulated such as septicaemia, hypotension, intra-abdominal and intra-pelvic sepsis, metastatic carcinoma, pre-existing liver disease, transfused blood, contamination of equipment or drug solutions with infected blood, or Australia antigen positive hepatitis. Liver biopsy when performed showed no specific histological features, and a picture similar to that of acute viral hepatitis was usual. It is impossible to exclude coincidental viral hepatitis.

It is difficult to reconcile these reports with the experience of Samrah (1963). He reported more than 400 triple exposures to halothane during irradiation of the cervix without jaundice or hepatic necrosis.

Trowell, Peto and Crampton-Smith (1975) studied patients having repeated anaesthetics during treatment of carcinoma of the cervix. In 18 patients, halothane was used repeatedly; four developed serum alanine aminotransferase activity of more than 100 i.u. litre^{-1} (8–35 i.u. litre^{-1}). In contrast, none of the 21 not given halothane did so. They concluded that in their study liver damage was more common in patients with carcinoma of the cervix after repeated halothane anaesthetics than after a variety of other commonly employed anaesthetic agents. Wright and others (1975) studied patients having repeated anaesthetics during treatment of carcinoma of the body of the uterus, cervix and bladder, and found that repeated administration of halothane given at short intervals was associated with an increased frequency of increased serum asparate aminotransferase activity. However, some of the controls had increased transaminase concentrations; therefore, it must be concluded that the reaction is not specific to halothane (Editorial, 1975). McEwan (1976) examined 41 patients undergoing repeated transurethral surgery who had received multiple halothane anaesthetics, first following an anaesthetic using halothane, and then following an anaesthetic without halothane. Disturbances of liver function, as assessed by serum alanine aminotransferase, asparate aminotransferase and lactic dehydrogenase activities, were greater after the second anaesthetic where halothane was not used.

Allen and Downing (1977) studied black females receiving radium therapy for carcinoma of the cervix under halothane anaesthetic. Fifty patients were exposed once, 16 received a second and six a third exposure to halothane. There were no significant changes from the control values in the serum concentrations of the transaminases or bilirubin. Allen and Downing (1978) pointed out that the report represents only a small part of their total experience of hundreds of cases of the use of halothane for radium treatment of carcinoma of the cervix.

In our study, three of 238 patients with carcinoma of the cervix became jaundiced during treatment. Two of the three received halothane at least twice. The other patient had an incomplete anaesthetic record, and might have had one exposure to halothane. Close examination of the records of these three jaundiced patients suggests pigment overload and sepsis as aetiological factors (Sherlock, 1975). Hepatocellular damage was not present and a toxic reaction to halothane could not be implicated. An editorial in the *Lancet* (Editorial, 1975) appeared to recommend that anaesthetists should act as though a cause and effect relationship " between postoperative jaundice, repeated halothane anaesthesia and radium treatment has now been established (from) a series of (three) papers from different parts of the world" (Hughes and Powell, 1970; Davis and Holdsworth, 1973; Moult and Sherlock, 1975).

The protagonists of the view that there is an association between jaundice following surgery, repeated halothane anaesthesia and radium treatment report nine instances of jaundice with two deaths in approximately 350 patients. Moult and Sherlock (1975) reported six instances of jaundice with one death in an unknown number of exposed patients. In 1976 a working party of the Medical Research Council concluded that unexplained jaundice might occur after multiple exposure to halothane, particularly if the re-exposure was within 28 days.

In 1976 Pratilas and Pratila, in a review of halothane hepatitis, recommended that repeated halothane anaesthesia be avoided during the treatment of carcinoma of the cervix.

Our experience, and that of Samrah (1963) and of Allen and Downing (1977) (reports totalling more than 500 patients in whom hepatitis was not seen), is sufficient to suggest that an association between postoperative jaundice and repeated halothane anaesthesia for radium therapy is not proven.

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HEPATITE CAUSEE PAR L'HALOTHANE CHEZ DES FEMMES SUBISSANT UN TRAITEMENT POUR CARCINOME DU COL DE L'UTERUS

RESUME

De 1964 à 1976, on a traité par irradiation et chirurgie, 238 patientes souffrant d'un carcinome du col de l'utérus. On a retrospectivement passé en revue leurs dossiers médicaux et trouvé que trois patientes avaient souffert de jaunisse après l'intervention chirurgicale, par suite de l'accumulation de pigments et de septicémie. L'exposition à l'halothane ne semble pas avoir été un facteur étiologique.

NEUERLICHE BETRACHTUNG VON HALOTHAN-HEPATITIS BEI FRAUEN, DIE FÜR ZERVIKALES KARZINOM BEHANDELT WERDEN

ZUSAMMENFASSUNG

Von 1964 bis 1976 wurden 238 Patientinnen mit zervikalem Krebs mit Bestrahlung und operativen Eingriffen behandelt. Ihre Krankengeschichten wurden ruckblickend betrachtet. Drei Patientinnen bekamen aufgrund von pigmentöser Überbelastung und von Sepsis Gelbsucht. Die Einwirkung von Halothan ergab keinen wesentlichen ätiologischen Faktor.

HEPATITIS CAUSADA POR HALOTANO EN MUJERES BAJO TRATAMIENTO DE CARCINOMA DEL CUELLO DEL UTERO

SUMARIO

De 1964 a 1976, recibieron tratamiento quirúrgico e irradiaciones 238 pacientes que padecían de carcinoma del cuello del útero. Sus antecedentes médicos fueron objeto de una revisíon retrospectiva. Trás pacientes tuvieron ictericia despúes de la operación por causa de una sobrecarga de pigmento y sepsis. No parece haber sido un factor etiológico significante el haber estado expuestas al halotano.

Br. J. Anaesth. (1979), **51**, 767

EFFECT OF MATERNAL POSITION ON FETAL HEART RATE DURING EXTRADURAL ANALGESIA

K. HUOVINEN AND K. TERAMO

SUMMARY

Using continuous cardiotocography, the effect of maternal position on fetal heart rate (FHR)was studied during extradural analgesia (EA) with either 50 or 100 mg of etidocaine without adrenaline for labour and vaginal delivery. Of 79 healthy parturients, 39 were supine and 40 were in the lateral position. FHR was normal in all patients during the control period before EA, and remained normal during EA in 53. Transient abnormal patterns occurred in 26 patients, 22 (56%) in the supine group and four (10%) in the lateral group, a significant difference ($P < 0.001$). The decrease in arterial pressure (AP), did not differ between the groups, but the frequency of abnormal FHR associated with a small or moderate decrease in AP (30% or less) was greater in the supine (51%) than in the lateral group (3%).

Extradural analgesia (EA) has been reported to have beneficial effects on mother and fetus and on the newborn infant (Pearson and Davies, 1974; Thalme, Belfrage and Raabe, 1974; Zador and Nilsson, 1974). However, continuous cardiotocographic recordings of the fetal heart rate (FHR) have revealed a varying number of abnormal FHR patterns in almost every series reported for this type of analgesia. There are few studies in which FHR changes have been absent (Thalme, Belfrage and Raabe, 1974). Usually, abnormal FHR patterns occur in less than 15% of fetuses (Printz and McMaster, 1972; Maltau, 1975; Jouppila et al., 1977), but on occasion between 20 and 50% (Schifrin, 1972), increasing to 77% (Zilianti et al., 1970). The main changes in FHR have been late deceleration or prolonged fetal bradycardia (Printz and McMaster, 1972; Schifrin, 1972; Maltau, 1975; Jouppila et al., 1977). There are reports of a loss of beat-to-beat variation (Boehm, Woodruff and Growdon, 1975; Raabe and Belfrage, 1976).

Both maternal hypotension (Brotanek et al., 1973; Maltau, 1975; Jouppila et al., 1977) and infusion of oxytocin during EA (Schifrin, 1972) have been shown to be associated with changes in FHR. The supine position has also been considered harmful to the fetus, especially during extradural block (Crawford, Burton and Davies, 1972). Many studies have described this for Caesarean section under general anaesthesia (Ansari et al., 1970; Crawford, Burton and Davies, 1972; Downing et al., 1974), but there is still little direct evidence of a harmful effect of the maternal supine position on the fetus during extradural block for vaginal delivery.

METHODS

Patients

We studied 79 healthy normotensive parturients with a single fetus in vertex presentation without signs of fetal distress. Sixty-eight mothers were primiparae and 11 multiparae. The maternal age ranged from 17 to 39 yr, the duration of gestation from 260 to 295 days and the cervical dilatation at induction of analgesia from 2 to 8 cm. All mothers were in the active phase of the first stage of labour (table I).

TABLE I. *Clinical data of patients in the supine and lateral position receiving lumbar extradural analgesia (EA) for labour with vaginal delivery*

	Supine ($n = 39$) Mean ± SD	Lateral ($n = 40$) Mean ± SD
Age (yr)	26 ± 4	25 ± 3
Gestation (days)	282 ± 9	280 ± 9
Cervical dilatation (cm)	4.8 ± 1.1	4.8 ± 1.3
Maternal arterial pressure before EA (mm Hg)		
Systolic	128 ± 13	122 ± 11
Diastolic	86 ± 9	82 ± 13

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Analgesia

Using a Portex catheter inserted in the extradural space at the L1–2 or L2–3 interspace, etidocaine (Duranest) 50 or 100 mg without adrenaline was administered in volumes of 5, 10 or 30 ml. The concentrations of etidocaine solutions ranged from 0.17 to 1%. The maternal position (supine or lateral) for induction of EA was selected at random (table II).

TABLE II. *Grouping of 79 parturients according to maternal position and amount of etidocaine injected for lumbar extradural analgesia (EA) for vaginal delivery*

Maternal position during EA	Amount of etidocaine without adrenaline (mg)	No. of parturients
Supine	100	12
Lateral	100	12
Supine	50	27
Lateral	50	28

Initially a 2.5-ml test dose was given and the remainder was administered over the succeeding 5–10 min. In the lateral group half the dose was given with the mother in one lateral position and the remainder with her in the contralateral position. These mothers remained in the lateral position during the entire period of study. The other patients remained supine before and during extradural block and for the whole period of EA, provided no maternal or fetal complication occurred (table II). If abnormal FHR changes were observed, the mother was turned immediately to a lateral position.

Fetal and maternal monitoring

FHR was monitored continuously using a scalp electrode, and uterine contractions were monitored with either an internal or an external tocometer (cardiotocographs: Hewlett-Packard, model 8020 A with transducer adapter 15137 or Corometrics Fetal Monitor, model III). FHR patterns were evaluated visually, decelerations according to Hon and Quilligan (1967), short-term base line variability (beat-to-beat) according to Hammacher (1969). In addition, serial fetal scalp capillary blood samples were obtained for pH and acid–base balance determinations (data published separately). Artefacts caused by fetal blood sampling on FHR were not taken into account.

We considered the FHR to be abnormal when there was late deceleration during two or more successive uterine contractions, bradycardia over two uterine contractions or over 5 min, and a loss of beat-to-beat variability under 5 beat min^{-1} for 10 min or longer (silent type of FHR base line variability).

Maternal arterial pressure (AP) was recorded by auscultation with an ordinary sphygmomanometer from the arm (upper arm in the lateral parturients) between uterine contractions at 5–10-min intervals.

The study commenced with a 30–60-min control period before the induction of EA. During this time the mother was in the same position as for the extradural injection. Oxytocin infusion was not given from 30 min before to 30 min after the induction. EA was given only if the FHR pattern was normal and maternal AP stable during the control period. Thus each parturient served as her own control before EA. If the mother's AP during EA decreased by more than 20 mm Hg, saline was infused i.v. at a rapid rate (1000 ml/15 min). No vasopressor was used.

Fisher's exact test between two frequencies and Student's unpaired *t* test between two means were used for statistical analyses.

RESULTS

Fetal heart rate (FHR)

FHR was normal in 53 of the 79 patients during EA (table III). Transient pathological FHR was observed in the remaining 26 patients, 22 of whom were supine and four were in the lateral position (table III). Typical examples are shown in figures 1, 2, 3 and 4.

TABLE III. *Type and frequency of fetal heart rate (FHR) changes during lumbar extradural analgesia in supine and lateral position*

FHR	Type of FHR changes	Frequency of FHR changes: Supine ($n = 39$)	Lateral ($n = 40$)
Normal	No changes	15 (38.5%)	34 (85.0%)
	Early decelerations	2 (5.1%)	2 (5.0%)
Abnormal	Late decelerations	21 (53.9%)	4(10.0%)
	Silent type of FHR base line variability	1 (2.6%)	0

These abnormal FHR changes commenced 8–23 min after the onset of EA and usually lasted 10–25 min, but occasionally longer (fig. 4). The frequency in the supine group (56%) was significantly different from that in the lateral group (10%) ($P < 0.001$).

The short-term variability of FHR, as judged by eye, remained unchanged in the 53 fetuses with

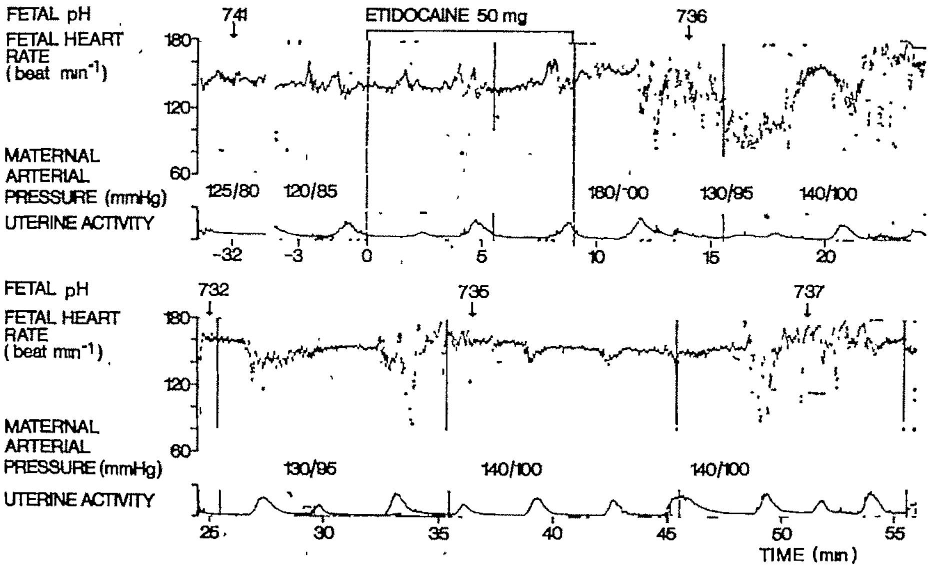

FIG. 1. Abnormal fetal heart rate (late deceleration type fetal bradycardia) associated with maternal supine position and unchanged maternal arterial pressure during lumbar extradural block induced by etidocaine 50 mg without adrenaline. (22-yr-old, para 1, 280th day of gestation, cervical dilatation 4 cm.) Bradycardia began 14 min after induction, associated with an increased beat-to-beat variability (saltatory type). It was followed at 25–48 min by a decrease in the short term variability. The fetal scalp capillary pH decreased from 7.41 to 7.32 unit in 25 min.

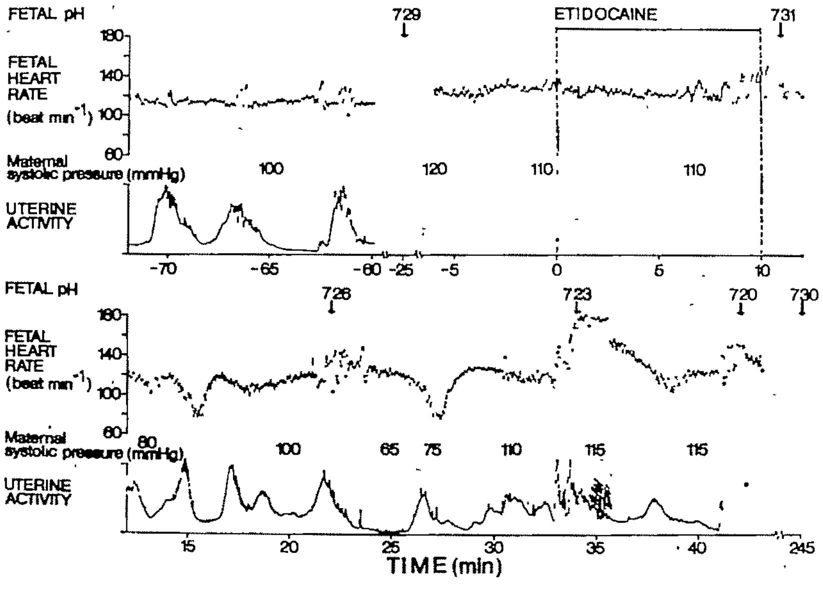

FIG. 2. Abnormal fetal heart rate (late decelerations) associated with supine position and maternal hypotension during lumbar extradural block induced by etidocaine 100 mg without adrenaline. (26-yr-old, para 1, 285th day of gestation, cervical dilatation 6 cm.) The late decelerations at 15 and 26 min after the block coincided with smallest maternal systolic pressures. The fetal scalp capillary blood pH decreased from 7.29 before the block to 7.20 unit 43 min after the induction.

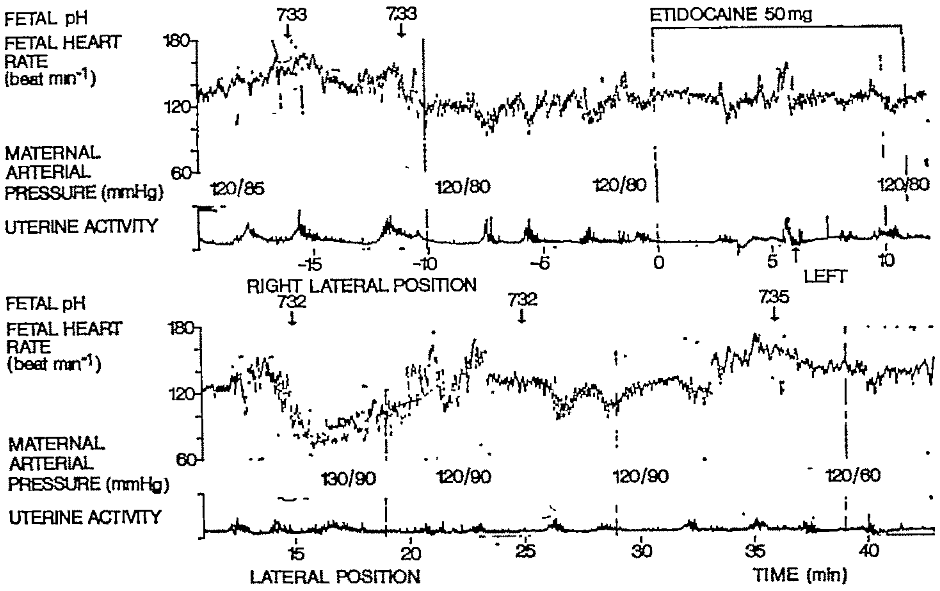

FIG. 3. Abnormal fetal heart rate (late deceleration type of bradycardia) associated with lateral recumbent position and unchanged arterial pressure during lumbar extradural block induced by etidocaine 50 mg without adrenaline. (19-yr-old para 1, 271st day of gestation, cervical dilatation 5 cm.) Bradycardia occurred 14 min after the induction, associated with an increased beat-to-beat variability. There are three consecutive late deceleration waves between 26 and 34 min. The fetal scalp capillary pH remained unchanged.

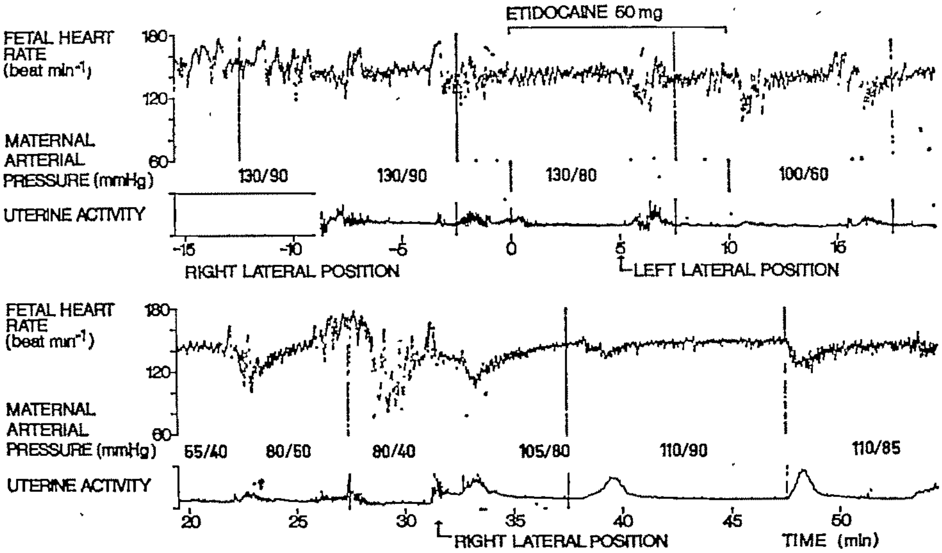

FIG. 4. Abnormal fetal heart rate (late decelerations) associated with maternal lateral recumbent position and maternal hypotension during lumbar extradural block induced by etidocaine 50 mg without adrenaline. (21-yr-old para 1, 266th day of gestation, cervical dilatation 4 cm.) Late decelerations beginning 16 min after the induction are visible over a period of 48 min. At 26–31 min they are associated with an increase and later at 32–48 min with a decrease in beat-to-beat variability.

normal FHR during EA. Eight of 26 fetuses with an abnormal heart rate during EA had a normal beat-to-beat variation, one had a silent pattern and the remaining 17 exhibited a saltatory pattern transiently (beat-to-beat variation more than 25 beat min^{-1}) alternating with normal short-term variability (figs 1, 3 and 4).

Maternal arterial pressure (AP)

The mean systolic AP before EA was similar in both groups (table II). The mean maximal decrease (± SD) in maternal AP during EA was 17 ± 17 mm Hg in the supine and 17 ± 16 mm Hg in the lateral group. In mothers with a normal FHR during EA the mean decrease in systolic AP was 18 ± 15 mm Hg in the supine group and 16 ± 17 mm Hg in the lateral. In mothers with an abnormal FHR during EA, the mean maximal decrease in systolic AP was not significantly different between the groups (18 ± 20 mm Hg supine, 28 ± 20 mm Hg lateral).

A decrease in systolic AP of more than 30% was observed in nine of the 79 patients (11.4%), five being lateral and four supine. The association of the decrease in maternal AP with the frequency of abnormal FHR changes is shown in table IV. When the systolic AP decreased more than 30% there were three fetuses of five with an abnormal heart rate in the lateral group in comparison with four of four in the supine group. The frequency of abnormal FHR during EA with etidocaine 50 mg was 12 of 27 (44.4%) compared with nine of 12 (75%) with etidocaine 100 mg in the group of supine mothers. In the lateral group the frequency of abnormal FHR was two of 28 fetuses (7.1%) with etidocaine 50 mg and two of 12 (16.7%) with 100 mg.

TABLE IV. *Degree of maternal hypotension and frequency of abnormal fetal heart rate (FHR) in supine and lateral position during extradural analgesia. *Number of fetuses with pathological FHR shown in parentheses*

Maternal position	n	Max. decrease of maternal systolic arterial pressure*	
		30% or less	more than 30%
Lateral	40	35 (1)	5 (3)
Supine	39	35 (18)	4 (4)
Total	79	70 (19)	9 (7)

The maximal decrease in systolic AP during EA with etidocaine 50 mg (10 ± 12 mm Hg) differed significantly from the corresponding decrease with 100 mg (21 ± 17 mm Hg) ($P < 0.005$).

DISCUSSION

Some authors describe EA as a safe technique for maternal analgesia (Zador and Nilsson, 1974; Raabe and Belfrage, 1976; Jouppila et al., 1977), although they noted the same types of abnormal FHR change during the block as occurred in the present study. These FHR changes probably indicated fetal asphyxia (Beard et al., 1971), but they were transient. Although the long-term effects of these FHR changes are unknown, it is obviously desirable that the frequency of pathological FHR changes should be as small as possible after EA.

In the present study the unfavourable fetal effects of the maternal supine position during obstetric EA were clearly demonstrated. Pathological FHR patterns were much more common in the supine position (56%) compared with the lateral recumbent position (10%). In three of the four fetuses developing a pathological FHR with the mother lateral, there was a marked decrease in maternal AP (table IV). A reduction in uterine placental blood flow (UPBF) as a result of hypotension was the probable cause of these FHR changes. Although the frequency of pathological FHR patterns during EA with etidocaine 100 mg was greater in both the supine and lateral group than with etidocaine 50 mg, it is likely that the FHR changes resulted from hypotension and not from a direct effect of the local anaesthetic on the fetus as hypotension was greater with 100 mg than with 50 mg of etidocaine. Infusion of a plasma expander immediately before the induction of EA has been shown to prevent the subsequent development of both maternal hypotension and a decrease in UPBF (Huovinen et al., 1977).

Vasoactive drugs should be used with great caution as they may diminish UPBF (Ralston, Shnider and de Lorimier, 1974), and this could harm the fetus further.

Human UPBF decreases synchronously with uterine contractions during EA (Brotanek et al., 1973). This may explain the observation that FHR changes during EA in the present study were mainly late decelerations (table IV) (figs 1, 2 and 4). Uterine hypertonus resulting from EA may also have been responsible for these pathological FHR changes, although hypertonus was not obvious.

Maternal hypotension during obstetric EA has been shown to increase the frequency of pathological FHR changes (Schifrin, 1972; Wingate et al., 1974). This was found in the present study (table IV), although the number of mothers with marked hypotension was small. The fetuses of supine mothers undergoing Caesarean section under general anaesthesia were considered at risk, even in those with minimal changes in maternal AP (Crawford, Burton and Davies, 1972). We confirmed this observation. Thus, when the decrease in AP was small (30% or less) abnormal FHR patterns occurred in 51% of the supine group while in the lateral group there was only one instance (fig. 3) (table IV). This emphasizes the fact that normal AP does not guarantee normal UPBF.

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EFFET DE LA POSITION MATERNELLE SUR LA FREQUENCE CARDIAQUE DU FOETUS PENDANT UNE ANALGESIE EXTRADURALE

RESUME

On a étudié à l'aide d'une cardiotocographie en continu l'effet de la position maternelle sur la fréquence cardiaque du foetus (FHR) pendant une analgésie extradurale (EA) administrée à l'aide de soit 50 soit 100 mg d'étidocaine sans adrénaline, pour le travail et l'accouchement par voie vaginale de 79 parturientes en bonne santé, dont 39 étaient couchées et 40 dans la position latérale. La FHR était normale chez toutes les patientes lors de la période de contrôle qui a précédé l'EA et elle est restée normale pendant l'EA chez 53 patientes. On a constaté sur 26 patientes des signes anormaux transitoires, 22 d'entre elles (56%) appartenant au groupe des femmes couchées et 4 (10%) appartenant au groupe latéral, différence significative ($P < 0,001$). La diminution de la pression artérielle (AP) n'a présenté aucune différence entre les groupes, mais la fréquence des FHR anormales associée à une diminution, modeste ou modérée, de l'AP (30% ou moins) a été plus importante dans la position couchée (51%) que dans le groupe latéral (3%).

WIRKUNG DER MÜTTERLICHEN POSITION AUF FÖTALE HERZTÄTIGKEIT WÄHREND EXTRADURALER ANALGESIE

ZUSAMMENFASSUNG

Mittels kontinuierlicher Herz-Tokographie wurde die Wirkung der mutterlichen Position auf die fotale Herztätigkeit (FHR) während extraduraler Analgesie (EA) mit entweder 50 oder 100 mg Etidocain ohne Adrenalin fur Wehen und vaginale Geburt studiert. Von 79 gesunden Gebärenden waren 39 in Rückenlage und 40 in lateraler Stellung. Bei allen Patientinnen war FHR wahrend der Kontrollperiode vor EA normal, und blieb normal wahrend EA bei 53 Patientinnen. Vorübergehende abnorme Erscheinungen ergaben sich bei 26 Patientinnen—22 davon (56%) in Ruckenlage und 4 (10%) in lateraler Stellung, also eine wesentliche Differenz ($P < 0{,}001$). Das Absinken des arteriellen Druckes (AP) unterschied sich in den einzelnen Gruppen nicht, doch war die Häufigkeit von abnormem FHR in Verbindung mit einem kleinen oder mässigen Anstieg von AP (30% oder weniger) höher in der Rückenlage (51%) als in der lateralen Gruppe (3%).

EFECTO DE LA POSICION MATERNAL SOBRE EL RITMO CARDIACO DEL FETO DURANTE ANALGESIA EXTRADURAL

SUMARIO

Se estudió el efecto de la posición maternal en el ritmo cardíaco del feto (RCF), mediante cardiotocografía continua, durante analgesia extradural (AE), con 50 ó 100 mg de etidocaina sin adrenalina, para parto y puerperio vaginal. De las 79 parturientes en buena salud, 39 estaban en supino y 40 en posición lateral. Durante el periodo de control antes de la AE, todas las pacientes tenían un RCF normal, él que se mantuvo normal durante la AE en 53 pacientes. Ocurrieron comportamientos anormales transitorios en 26 pacientes, 22 (56%) del grupo en supino y 4 (10%) en el grupo lateral, lo que constituye una diferencia significativa ($P < 0{,}001$). La disminución de la presión arterial (PA) no difirió entre los grupos, pero la frecuencia del RCF anormal asociado con una reducción moderada o baja de la PA (30% o menos) era mayor en el grupo en supino (51%) que en el grupo lateral (3%).

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HAS DROPERIDOL AN ATROPINIC EFFECT?

P. PARMENTIER AND P. DAGNELIE

SUMMARY

The action of droperidol on the tachycardia produced by atropine and on the serum concentration of cholinesterases was observed during balanced anaesthesia. Without atropine, the mean heart rates of patients who received fentanyl or fentanyl plus droperidol were similar. Atropine increased heart rate only in the presence of droperidol ($P < 0.001$) (fentanyl *v.* fentanyl plus droperidol: $P < 0.05$). Droperidol inhibited serum cholinesterases ($P < 0.05$); this effect was independent of atropine.

Some authors claim that butyrophenones have no anti-muscarinic action (Janssen et al., 1963); others that there is a weak anti-muscarinic effect (Byck, 1975; Stanley, 1978). We observed the effect of droperidol on the tachycardia produced by atropine, and on the serum cholinesterase concentrations during anaesthesia with nitrous oxide and fentanyl.

METHODS

Twenty-four unselected adults of either sex, free from cardiac disease, were studied during elective surgery. Premedication was with diazepam 10 mg i.m. After 30 min thiopentone 3.5 mg kg^{-1} followed by suxamethonium 1 mg kg^{-1} were given i.v. The trachea was intubated and the lungs were ventilated mechanically with 40% oxygen in nitrous oxide. Twelve patients received fentanyl 0.003 mg kg^{-1} i.v. and 12 received fentanyl 0.003 mg kg^{-1} plus droperidol 0.15 mg kg^{-1}.

Each group of 12 was separated randomly into subgroups of six who received either atropine 0.007 mg kg^{-1} i.v. 5 min after the induction of anaesthesia or no treatment. The heart rate (displayed on an electrocardioscope) was recorded for 4 min. All observations were made before surgery, the patients being free from external stimulation. The minute volume of ventilation was determined using the Engström nomogram (Engström and Herzog, 1959).

Commercial drug preparations were used. Linear regression coefficients of heart rate against time were computed for each patient, and these coefficients were submitted to a two-way analysis of variance (Dagnelie, 1973).

In a second study of 28 patients, grouped and treated as in the first study, atropine was injected at the time of induction of anaesthesia rather than 5 min later. Venous blood was sampled immediately before induction for the determination of cholinesterase activity (control). A second sample was taken 10 min later. Less than 50 ml of saline was administered i.v. between sampling times. A Biochemica test kit (Boerhinger & Soehne, Mannheim) was used to measure the activity of cholinesterase by a colourimetric method (Ellman et al., 1961). The rate of production of thiocholine was measured as acetylthiocholine was hydrolysed. Thiocholine reacted with dithiobisnitrobenzoate ion to produce a yellow anion of 5-thio-2-nitro-benzoic acid.

Linear regression coefficients of cholinesterase concentration against time were computed for each patient; these coefficients were submitted to a two-way analysis of variance (Dagnelie, 1973).

RESULTS

In the absence of atropine the heart rates of patients who received either fentanyl or fentanyl plus droperidol were similar (table I; fig. 1). Atropine significantly increased the heart rate ($P < 0.001$) only in the presence of fentanyl plus droperidol.

Droperidol inhibited the cholinesterases ($P < 0.05$) both in the presence of atropine and in its absence (table II). Atropine did not influence the cholinesterase concentration significantly and it did not affect the action of droperidol on cholinesterase.

DISCUSSION

Droperidol enhanced the anti-muscarinic effect of atropine upon heart rate.

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TABLE I. *Variation in mean heart rate (beat min^{-1} ± SEM) of four subgroups of six patients with and without atropine* 0.007 *mg kg^{-1}, or receiving either fentanyl* 0.003 *mg kg^{-1} or fentanyl* 0.003 *mg kg^{-1} plus droperidol* 0.15 *mg kg^{-1}. The statistical significance of the differences between the subgroups is indicated. $p = a+bt$: Equation of the best fitting line joining the corresponding group of means*

	Fentanyl					Statistical significance	Fentanyl + droperidol				
Minutes after atropine	0	1	2	3	4		0	1	2	3	4
Mean (beat min^{-1})	69.2	66.3	65.5	64.8	63.8		70.2	68.7	66.0	64.3	63.7
±SEM	±3.7	±3.3	±3.4	±3.0	±2.6	←n.s.→	±2.6	±1.9	±2.4	±2.2	±2.2
$p = a+bt$	$p = 68.37-1.22t$						$p = 70.03-1.73t$				
Statistical significance	↕ n.s.						↕ $P < 0.001$				
	Fentanyl + atropine 0.007 mg kg^{-1}						Fentanyl + droperidol + atropine 0.007 mg kg^{-1}				
Minutes after atropine	0	1	2	3	4		0	1	2	3	4
Mean (beat min^{-1})	71.5	72.8	72.0	71.2	71.0		69.7	76.0	76.7	75.5	75.2
±SEM	±2.8	±4.0	±4.2	±4.3	±3.8	←$P < 0.05$→	±2.9	±4.3	±4.4	±4.9	±4.8
$p = a+bt$	$p = 72.83-0.27t$						$p = 72.50+1.05t$				

TABLE II. *Mean variations (mu. ± SEM) of the serum cholinesterases of four subgroups, of seven patients each,* 10 *min after the administration of one of the following combinations of drugs: fentanyl* 0.003 *mg kg^{-1}; fentanyl* 0.003 *mg kg^{-1} + droperidol* 0.15 *mg kg^{-1}; fentanyl* 0.003 *mg kg^{-1} + droperidol* 0.15 *mg kg^{-1} + atropine* 0.007 *mg kg^{-1}; fentanyl* 0.003 *mg kg^{-1} + atropine* 0.007 *mg kg^{-1}. The statistical significance of the differences between the subgroups is indicated*

	Fentanyl	Statistical significance	Fentanyl + droperidol
Mean variation of cholinesterase concn from control ±SEM	−27 mu. (−1.2%) ±65	←$P < 0.05$→	−206 mu. (−7.7%) ±96
Statistical significance	↕ n.s.		↕ n.s.
	Fentanyl + atropine 0.007 mg kg^{-1}		Fentanyl + droperidol + atropine 0.007 mg kg^{-1}
Mean variation of cholinesterase concn from control ±SEM	−70 mu. (−3.2%) ±77	←$P < 0.05$→	−357 mu. (−14.9%) ±109

Two aspects of the programme of study may compromise the conclusions. The effect of fentanyl, droperidol and atropine on heart rate was studied in patients who were receiving other drugs: diazepam, thiopentone, suxamethonium and nitrous oxide. On the other hand, it appeared from our results that a stable heart rate was not achieved when atropine was injected. The demonstration that fentanyl and droperidol exert their maximal effect within 5 min (Edmond-Seal and Prys-Roberts, 1970; Price, 1975) justified our choice of a 5-min interval between either fentanyl or fentanyl–droperidol and atropine.

Droperidol increases heart rate (Schaper, Jageneau and Bogaard, 1963; Morrison, Clarke and Dundee, 1970; Ferrari et al., 1974), and this effect is generally attributed to a reflex response following

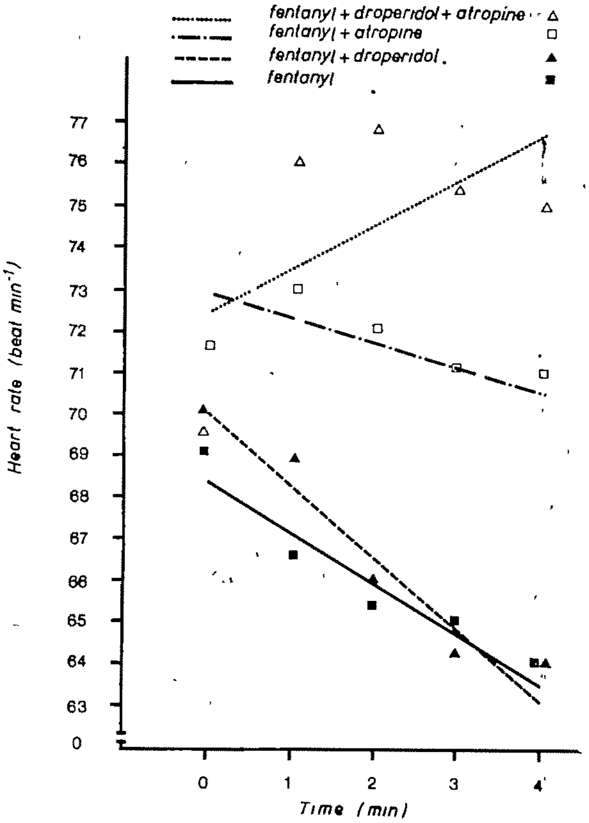

FIG. 1. Variations in mean heart rate of four groups of six patients, either in the presence of atropine 0.007 mg kg^{-1} or in its absence, after either fentanyl 0.003 mg kg^{-1} or fentanyl 0.003 mg kg^{-1} plus droperidol 0.15 mg kg^{-1}. (SEM are shown in table I).

small reductions in arterial pressure (Schaper, Jageneau and Bogaard, 1963).

The addition of a baroreflex to the anti-muscarinic action of atropine is improbable, since in the absence of atropine the heart rate of the patients who received fentanyl did not differ from the rate of those who received fentanyl plus droperidol. For the same reason a difference in vagal tone which could explain a stronger effect of atropine upon heart rate of one group as compared with another (Innes and Nickerson, 1975) is difficult to accept. A mild anti-muscarinic effect of droperidol is not incompatible with our observation. A small amount of atropine may have no effect upon heart rate or may even decrease it (Innes and Nickerson, 1975).

We can exclude the role of anxiety following the use of droperidol (Morrison, Clarke and Dundee, 1970) since our patients were asleep.

Droperidol was the only drug which inhibited the serum cholinesterases (table II). Fortes, Scivoletto and Reis (1978) have demonstrated the anticholinesterase activity of droperidol and other butyrophenones. Todrick (1954) showed the selective affinity to serum cholinesterases of drugs with an anti-muscarinic action.

We conclude that droperidol may have a mild atropinic action as this drug increases heart rate (Schaper, Jageneau and Bogaard, 1963; Morrison, Clarke and Dundee, 1970; Ferrari et al., 1974) provokes mental restlessness (Morrison, Clarke and Dundee, 1970; Ferrari et al., 1974), inhibits the increase of bronchial tone after fentanyl (Yasuda et al., 1978), enhances the anti-muscarinic effect of atropine on heart rate (table I and fig. 1) and inhibits serum cholinesterases (Fortes, Scivoletto and Reis, 1978) (table II). It may be added that haloperidol, a closely related drug, causes blurring of vision (Byck, 1975).

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LE DROPERIDOL A-T-IL UN EFFET ATROPINIQUE?

RESUME

L'action du dropéridol sur la tachycardie produite par l'atropine et sur les concentrations de cholinestérases dans le sérum a été observée au cours d'une anesthésie équilibrée. Sans atropine, les fréquences cardiaques moyennes des malades ayant reçu du fentanyl ou du fentanyl additionné de dropéridol ont été similaires. L'atropine n'a augmenté la fréquence cardiaque qu'en présence de dropéridol ($P < 0{,}001$) (fentanyl *v.* fentanyl plus dropéridol: $P < 0{,}05$). Le dropéridol a modéré les cholinestérases dans le sérum ($P < 0{,}05$); cet effect étant indépendant de l'atropine.

HAT DROPERIDOL EINEN ATROPIN-EFFEKT?

ZUSAMMENFASSUNG

Die Wirkung von Droperidol auf die von Atropin bewirkte Tachykardie und auf die Serumkonzentration von Cholinesterase wurde während einer ausgewogenen Narkose beobachtet. Ohne Atropin waren die mittleren Herzminutenvolumen gleich bei Patienten, die entweder Fentanyl oder Fentanyl plus Droperidol erhalten hatten. Atropin erhohte das Herzminutenvolumen nur zusammen mit Droperidol ($P < 0{,}001$) (Fentanyl gegenüber Fentanyl plus Droperidol: $P < 0{,}05$); Droperidol unterdrückte Serumcholinesterasen ($P < 0{,}05$); diese Wirkung war unabhängig von Atropin.

TIENE EL DROPERIDOL UN EFECTO ATROPINICO?

SUMARIO

Se observó la acción del droperidol en la taquicardia producida por atropina y en la concentración de colinesteresas en el suero durante anestesia equilibrada. Sin atropina, eran similares los ritmos cardíacos medios de los pacientes que recibieron fentanilo o fentanilo más droperidol. La atropina producía un aumento del ritmo cardíaco, únicamente en presencia de droperidol ($P < 0{,}001$) (fentanilo *c.* fentanilo más droperidol: $P < 0{,}05$). El droperidol inhibió las colinesterasas del suero ($P < 0{,}05$); este efecto era independiente de la atropina.

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VENOUS SEQUELAE FOLLOWING ETOMIDATE

M. Zacharias, R. S. J. Clarke, J. W. Dundee and S. B. Johnston

SUMMARY

Five hundred patients receiving one of three different formulations of etomidate were observed on the 2nd and 3rd days after operation for possible venous sequelae. The total frequency of sequelae was 8% or more, the greatest being with the propylene glycol formulation (23%). Formulation of the drug and total dose employed were the most important factors influencing venous sequelae, which were not related to pain on injection.

Thrombosis and thrombophlebitis can occur following any i.v. anaesthetic agent. The frequency is small after thiopentone (Hutton and Hall, 1957; Hewitt et al., 1966), methohexitone (Hewitt et al., 1966) and Althesin (Carson et al., 1972) and greater after propanidid (O'Donnell, Hewitt and Dundee, 1969) and "narcotal" (Gjores, 1958). However, only with hydroxydione (Dent, Wilson and Stephen, 1956; Taylor and Shearer, 1956; Robertson and Wynn-Williams, 1961) and G 29 505 (Riding et al., 1963) has venous irritation been the main reason for the drug being withdrawn from clinical use. The venous sequelae may be caused by chemical or osmotic irritation (Stedtfeld, 1957) and the frequency is greater the higher the concentration of the drug (O'Donnell, Hewitt and Dundee, 1969) and the greater the dose (Robertson and Wynn-Williams, 1961).

It has been reported that etomidate produces a small frequency of venous sequelae (Bruckner et al., 1974; Morgan, Lumley and Whitwam, 1975; Gooding and Corssen, 1976; Holdcroft et al., 1976; Popescu, 1976; Van de Walle et al., 1976). However, it causes pain on injection and organic solvents are used in some of the later formulations of the drug, factors which suggest that there may be an appreciable frequency of venous sequelae. The present study was carried out to investigate the frequency of venous irritation following the different preparations of the drug and to study the influence of the speed of injection on this frequency.

METHODS

The method used was based on that employed in this department in earlier studies of venous sequelae following i.v. anaesthetic agents (Hewitt et al., 1966; O'Donnell, Hewitt and Dundee, 1969). Five hundred patients undergoing surgical or gynaecological procedures were studied. They were of either sex and their ages ranged from 10 to 80 yr. The aqueous (0.15%), polyethylene glycol (0.2%) and propylene glycol (0.2%) formulations of etomidate were used. The drug was injected either rapidly (2 mg s^{-1}) or slowly (1 mg s^{-1}) in doses of 0.3 mg kg^{-1} or more. The division of patients into these groups is shown in table I; there were at least 50 patients in each group. A 21-s.w.g indwelling needle was used and pain on injection was elicited by employing the method described previously (Zacharias et al., 1978). Further increments of the drug were given as required. No other drug was injected into the same vein, no infusions set up nor any tourniquet applied to the same arm. The site and size of the vein, time the needle remained in the vein, speed of injection and total dose used were recorded. Patients in whom extravasation of blood occurred were excluded from the study.

The patients were seen on the 2nd and 3rd days following the anaesthetic and the site of injection examined for the occurrence of: phlebitis—tenderness on palpation of the vein; thrombosis—hardness of the vein; thrombophlebitis—tender and hard vein. Lesions of less than 2 cm were classed as "localized" while those of more than 2 cm were "extended".

Data from previous studies in this department were used for comparison.

RESULTS

Table I shows the frequency of venous sequelae following etomidate in the various groups. The two

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TABLE I. *Details of the various groups and the results obtained up to the 3rd day after operation. (*For criteria see text)*

				Percentage frequency of venous sequelae						
				Phlebitis		Thrombosis		Thrombophlebitis		
Formulation	Concn (%)	Speed of injection*	*n*	Localized	Extended	Localized	Extended	Localized	Extended	Total
Aqueous	0.15	Slow	129	2.3	0.8	4.7	0.8	0.7	0	9.3
	0.15	Fast	98	0	0	9.2	0	2.0	1.0	12.2
Polyethylene	0.2	Slow	52	0	0	5.8	0	1.9	0	7.7
glycol	0.2	Fast	52	5.8	0	0	0	1.9	0	7.7
Propylene	0.2	Slow	79	1.3	2.6	5.1	1.3	6.4	3.8	20.5
glycol	0.2	Fast	90	1.1	1.1	10.0	7.8	0	5.6	25.6

prominent features are the great frequency following the propylene glycol formulation of the drug and also the great frequency of extended thrombophlebitis with that formulation. The frequency of venous sequelae with the aqueous and propylene glycol formulations was greater with the faster speed of injection, but when the three groups were pooled this difference was not significant ($\chi^2 = 1.16$; $P > 0.05$).

Figures 1 and 2 show the various factors which could influence venous sequelae following etomidate. For the purpose of analysis we have pooled the data and analysed each factor in turn in order to find out any influence of that particular factor on the study. The size or site of the vein, the duration of the needle *in situ* and the age of the patient are not important factors. However, it is clear that the sequelae are related to the formulation and the total dose of the drug used (36.8% in doses greater than 0.9 mg kg^{-1} as compared with 12.8% in doses up to 0.3 mg kg^{-1}).

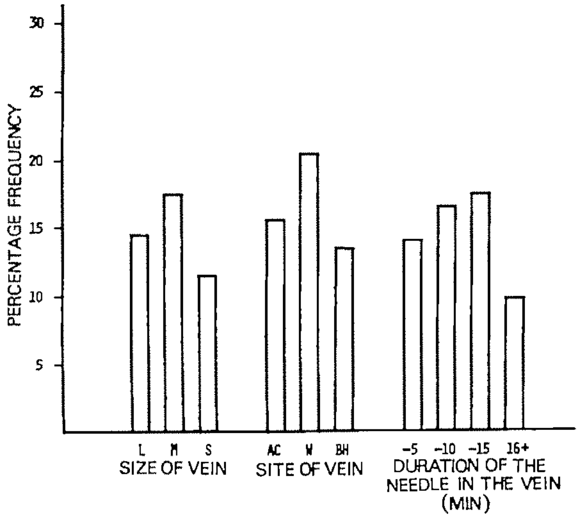

FIG. 1. Factors influencing venous sequelae following etomidate: size of veins (large (L), moderate (M) and small (S)); site of injection (antecubital fossa (AC), wrist (W) and back of hand (BH)).

Since etomidate causes a high frequency of pain on injection, the relationship of this to venous sequelae was studied also. However, no conclusive association between pain and venous sequelae could be demonstrated on the pooled data ($\chi^2 = 1.706$; $P > 0.05$).

It has been shown that venous sequelae following i.v. agents appear to increase for up to 7–10 days after anaesthesia with diazepam (Hegarty and Dundee, 1978). Therefore, we examined a small group of patients on the 14th day, in addition to 2–3 days' follow-up (table II). This was only possible in patients receiving large doses of the propylene glycol formulation (average doses of 1.2 ± 0.3 mg kg^{-1}), which may explain the high frequency of venous sequelae (55% on the 3rd day). As with other studies, this showed a greater frequency of extended thrombosis at the end of 2 weeks, but no evidence of infection.

TABLE II. *Venous sequelae following propylene glycol formulation of etomidate in 20 patients followed up to the 14th day following administration*

		Percentage frequency	
		3rd day	14th day
Phlebitis	Localized	0	0
	Extended	0	0
Thrombosis	Localized	15	15
	Extended	5	30
Thrombophlebitis	Localized	20	0
	Extended	15	0
Total venous sequelae		55	45

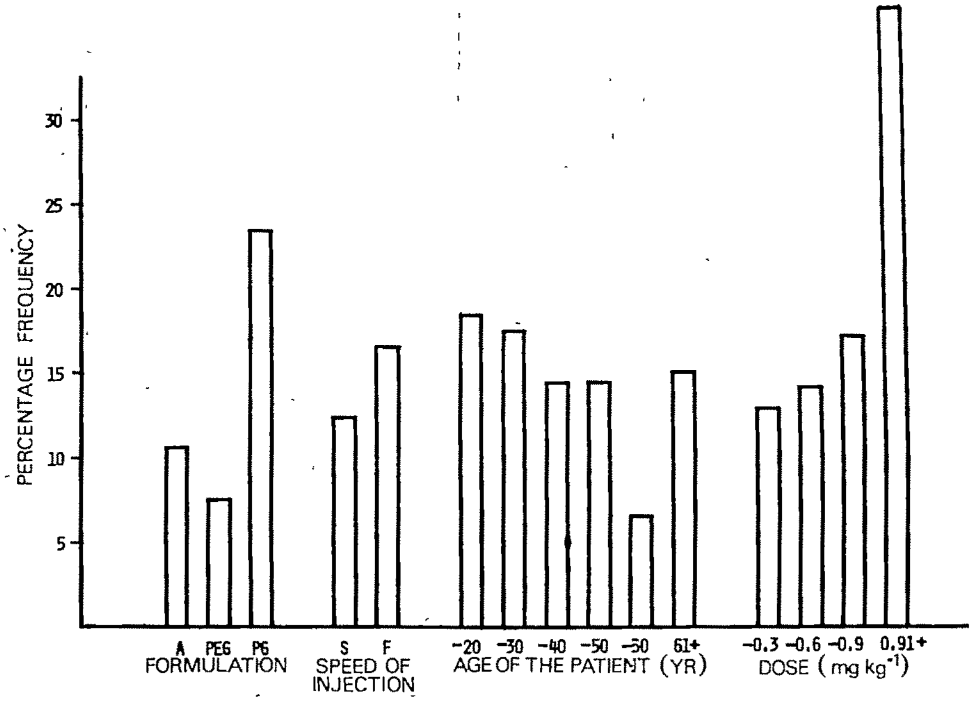

FIG. 2. Factors influencing venous sequelae following etomidate: formulation (aqueous (A), polyethylene glycol (PEG) and propylene glycol (PG)); speed of injection (slow (S) and fast (F)); age of patient; dose.

The frequency of venous sequelae was great following all the formulations of etomidate, in comparison with other common i.v. anaesthetic agents (table III). Analysis of the combined data of both slow and fast speeds of injection gave a significantly greater frequency of sequelae with the propylene glycol formulation of the drug than with the aqueous ($\chi^2 = 7.92$; $P < 0.005$) and polyethylene glycol ($\chi^2 = 8.23$; $P < 0.005$) formulations. Also, the frequency of venous sequelae was greater in the case of the aqueous formulation of etomidate than with thiopentone ($\chi^2 = 11.42$; $P < 0.001$), methohexitone ($\chi^2 = 8.37$; $P < 0.005$), or Althesin ($\chi^2 = 11.56$; $P < 0.001$). The polyethylene glycol formulation was associated with greater frequency of sequelae than thiopentone ($\chi^2 = 5.40$; $P < 0.025$) and Althesin ($\chi^2 = 3.89$; $P < 0.05$), whereas with propylene glycol formulation of etomidate the frequency was greater than with thiopentone ($\chi^2 = 31.41$; $P < 0.0005$), methohexitone ($\chi^2 = 27.30$; $P < 0.0005$), propanidid ($\chi^2 = 10.99$; $P < 0.001$) and Althesin ($\chi^2 = 39.61$; $P < 0.0005$).

TABLE III. *Frequency of venous sequelae following etomidate and other i.v. anaesthetic agents. †Significantly greater frequency than with thiopentone, methohexitone and Althesin; ‡ significantly greater frequency than with thiopentone and Althesin; § significantly greater frequency than all others. *Data from O'Donnell, Hewitt and Dundee (1969); **data from Carson and others (1972)*

Drug	*n*	Concn (%)	Percentage frequency of all sequelae
Etomidate (aqueous)	227	0.15	10.8†
Etomidate (polyethylene glycol)	104	0.2	7.7‡
Etomidate (propylene glycol)	169	0.2	23.1§
Thiopentone*	202	2.5	2.0
Methohexitone*	203	1.0	3.0
Propanidid*	618	5.0	11.3
Althesin**	330	1.2	3.0

DISCUSSION

The reported frequency of venous sequelae for the various i.v. anaesthetic agents varies widely. In the light of experience with hydroxydione it is imperative that the frequency of venous sequelae following any new i.v. anaesthetic agent should be known at an early stage in the clinical trials.

Previous studies with etomidate report only a small frequency of venous sequelae, and the reported frequency varied from no sequelae to about 2% and was mostly transient in nature. Contrary to published data, our method of observation showed a frequency which was significantly greater than with many of the commonly-used i.v. agents, especially with the propylene glycol formulation (23%); this high frequency may make that particular formulation unacceptable clinically.

There are many possible causes of the venous sequelae. Injury to the vein wall by the needle can cause thrombosis (Hutton and Hall, 1957), as can chemical and osmotic irritation (Stedtfeld, 1957). Irritation can result from mechanical causes because of the large volume of the drug injected and perhaps from repeated injections. Osmotic irritation may be important with the propylene glycol formulation of etomidate, which has an osmotic pressure of about 4645 mosmol kg^{-1} (Hendry, Miller and Lees, 1977). It is possible that the vein wall comes into contact with a greater concentration of the drug during a rapid injection compared with a slower one. With other drugs dilution of a drug into a rapidly running infusion has been shown to reduce the frequency of venous sequelae (Dent, Wilson and Stephens, 1956; Landau, 1958).

Pain on injection is unpleasant to the patient. Presumably it may, in part, be a result of direct chemical irritation of the intima. However, we were unable to show a correlation between the venous sequelae and pain on injection.

Because of the narrow range of concentration available we were unable to study the effect of concentration of the drug on venous sequelae. With hydroxydione and G 29 505, concentration did not play an important part in the sequelae (Robertson and Wynn-Williams, 1961; Riding et al., 1963). However, with thiopentone, methohexitone and propanidid, dilution reduced the frequency of venous sequelae (Hewitt et al., 1966; O'Donnell, Hewitt and Dundee, 1969).

The frequency of venous sequelae increases with age in the case of some i.v. anaesthetics (Robertson and Wynn-Williams, 1961) and diazepam (Hegarty and Dundee, 1978). We were not able to show a correlation between age and the frequency of sequelae, probably because of disproportionately greater numbers of younger patients in this study.

The frequency of venous sequelae is dose-related (Robertson and Wynn-Williams, 1961; Podlesch and Zindler, 1965). It is demonstrated clearly in figure 2 that doses greater than 0.9 mg kg^{-1} cause a frequency greater than 37%.

The small number of patients in whom a 2-week follow-up was carried out shows the transient nature of phlebitis, and an increase in the frequency of extended thrombosis following the appearance of this sequel. However, in contrast to the findings with diazepam (Hegarty and Dundee, 1978) there was no significant increase in the overall frequency of the total venous sequelae by the 2nd week.

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SEQUELLES VEINEUSES APRES ADMINISTRATION D'ETOMIDATE

RESUME

On a observé 500 patients auxquels on avait administré de l'étomidate, préparé selon l'une de trois formules différentes, les deuxième et troisième jours qui ont suivi l'intervention chirurgicale, pour voir s'ils auraient des séquelles veineuses. La fréquence totale de séquelles a été de 8% et même davantage, la plus importante étant celle causée par la formule propylène glycol (23%). La formule du médicament et la dose totale utilisées ont été les facteurs les plus importants influençant les séquelles veineuses, lesquelles n'ont eu aucun rapport avec la douleur causée par l'injection.

VENÖSE FOLGEERSCHEINUNGEN NACH ETOMIDAT

ZUSAMMENFASSUNG

Fünf hundert patienten, die eine von drei verschiedenen Formeln von Etomidat erhalten hatten, wurden am zweiten und dritten Tag nach der Operation auf mogliche venose Folgeerscheinungen beobachtet. Die Gesamthäufigkeit dieser Erscheinungen war 8% oder mehr, an hochsten mit der Propylen-Glycol-Formel (23%). Die Formulierung der Droge und die Gesamtdosis waren die wichtigsten Faktoren durch die venöse Folgeerscheinungen beeinflusst wurden, soweit diese nicht mit dem Injektionsschmerz in Zusammenhang standen.

SECUELA VENOSA SIGUIENDO LA ADMINISTRACION DE ETOMIDATA

SUMARIO

Quinientos pacientes que recibieron una de tres formulaciones diferentes de etomidata fueron observados en el segundo y tercero día después de la operación, en busca de una posible secuela venosa. La frecuencia total de la secuela fue de 8% o más, produciéndose la mayor con la formulación de propilenglicol (23%). La formulación de la droga y la dosis total empleada fueron los factores más importantes que influenciaron la secuela venosa, que no se relacionaron al dolor de la inyección.

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MORBIDITY IN GYNAECOLOGICAL DAY-CASE SURGERY

A comparison of two anaesthetic techniques

T. M. HUNT, O. M. PLANTEVIN AND J. R. GILBERT

SUMMARY

The effectiveness of fentanyl, given as part of the anaesthetic technique, in reducing abdominal pain following outpatient gynaecological surgery has been examined. It was found to reduce significantly the frequency of abdominal pain in the period extending from discharge from hospital to the first evening, while not compromising surgical conditions nor increasing the frequency of other postoperative sequelae such as nausea and vomiting.

Day-case surgery is practised increasingly both for economic reasons and for the convenience of the patient. However, Fahy and Marshall (1969) have reported a high frequency of morbidity after surgery, extending often into the 2nd day after operation, and a recent study of patients undergoing minor gynaecological surgery as day cases demonstrated that abdominal pain was a common complaint following surgery (Towey et al., 1979).

The present study was designed to investigate whether the inclusion of a powerful short-acting analgesic in the anaesthetic technique could reduce the frequency of this complaint. Two simple anaesthetic techniques were compared; one technique included the analgesic fentanyl, while the other used halothane as the main agent.

METHODS

One hundred and three patients undergoing dilatation and curettage of the uterus in the outpatient theatre at St Thomas's Hospital were studied. Patients were assessed before operation by the anaesthetist and those not considered suitable for day-case surgery for medical or social reasons, and those receiving tranquillizer or anti-depressant drugs were excluded. No premedication was given and surgery took place in the morning. The same medical and nursing staff were involved throughout the study. Patients were allocated randomly to one of two groups: in *group H* anaesthesia was induced with 1% methohexitone 60–100 mg and maintained with 60% nitrous oxide in oxygen with halothane 1% as necessary. In *group F* a single dose of fentanyl calculated on a weight basis was given i.v. immediately before induction. Patients weighing between 50 and 70 kg received 100 μg; those weighing less than 50 kg received 75 μg and those weighing more than 70 kg, 125 μg. Anaesthesia was induced with 1% methohexitone 60–100 mg and maintained with 60% nitrous oxide in oxygen and incremental doses of methohexitone (to a total of 100 mg). The time of induction and the time of completion of the procedure were recorded, as was the occurrence of minor complications such as hiccup or cough. No major complications were observed. Each patient recovered from the anaesthetic on a trolley and the time at which she opened her eyes in response to her name was recorded. The occurrence of nausea, vomiting, abdominal pain and other symptoms was noted and two tablets of Distalgesic (dextropropoxyphene 65 mg and paracetamol 650 mg) was prescribed for the relief of pain if necessary. Antiemetics were not given unless repeated vomiting occurred. The patients were usually fit to go home with an escort about 3 h after the operation and just before leaving the hospital each patient was asked to complete a questionnaire recording the presence or absence of each of the following sequelae: abdominal pain, backache, headache, nausea, vomiting, drowsiness, dizziness and muscle ache. In addition the patient was given three further questionnaires to be completed on the 3rd evening after operation and returned to the hospital by post. These sought the occurrence of the same symptoms during the following periods: the remainder of the day and evening of operation, the first day after operation and the second day after operation.

Chi-square test was used to evaluate the significance of differences between the groups.

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TABLE I. *Frequency (number and per cent) of symptoms and complications at the four times of enquiry. H = halothane group; F = fentanyl group.* † = *not significant;* **$P < 0.05$*

	Day of operation							
	Before discharge		At home		1st day after op.		2nd day after op.	
Symptom	H ($n = 47$)	F ($n = 56$)	H ($n = 43$)	F ($n = 54$)	H ($n = 43$)	F ($n = 54$)	H ($n = 43$)	F ($n = 54$)
Abdominal pain	29 62	24 43	27 63	23 43	23 53	25 46	16 37	20 37
χ^2	3.6330†		3.9101*					
Backache	12 26	6 11	19 44	15 28	21 49	18 33	20 47	16 30
χ^2	3.8904*							
Headache	17 36	20 36	18 42	22 41	15 35	21 39	11 26	13 24
Nausea	14 30	24 43	14 32	17 31	10 23	13 24	6 14	5 9
χ^2	1.8786†							
Vomiting	4 9	11 20	3 7	9 17	3 7	1 2	2 5	0 0
χ^2	2.5452†		2.0734†					
Drowsiness	26 55	35 62	32 74	40 74	22 51	18 33	11 26	9 17
χ^2	0.5456†							
Dizziness	19 40	26 46	16 37	23 43	12 28	16 30	10 23	10 19
Muscle ache	3 6	5 9	7 16	12 22	10 23	12 22	10 23	5 9
Need for analgesia	12 26	7 12	21 49	16 30	17 40	17 31	13 30	16 30
χ^2	2.885†		3.7431†					

RESULTS

Ninety-seven patients returned the postal questionnaires: 43 in group H and 54 in group F. One hundred and three patients were available for study in the periods of operation and immediately after operation: 47 in group H and 56 in group F.

There were no statistically significant differences between the groups in respect of age, weight, duration of operation, total time asleep and operating conditions.

The frequency and timing of the various symptoms are shown in table I. Abdominal pain was a common complaint occurring in 52% of patients before discharge, 53% later that day and 49% by the following day. Fewer patients in group F complained of abdominal pain on the day of operation while in hospital and after returning home, although statistical significance was achieved only during the latter period ($P < 0.05$). In addition, significantly fewer patients in group F complained of backache in the first hours after operation ($P < 0.05$). The requirements for analgesia were not significantly different in the two groups at any stage following operation. There was no increase in the frequency of nausea and vomiting in group F, although two patients in this group required metoclopramide 10 mg to control repeated vomiting. The frequency of headache, dizziness, drowsiness and muscle ache was comparable in the two groups.

DISCUSSION

The ideal anaesthetic technique for short outpatient procedures is one that allows the patients to waken as soon as possible and which has minimal after-effects of either the surgery or the anaesthetic. Unfortunately, techniques which allow quick awakening, such as a single dose of methohexitone or Althesin, frequently do not afford any residual analgesia, while the use of an opiate tends to prolong the period of recovery. Recently doubt has been cast on whether fentanyl is short-acting; certainly its hypnotic action is short-lived (Foldes, Shiffman and Knofeld, 1970), but its analgesic and respiratory depressant action are little different from equi-analgesic doses of morphine and phenoperidine (Rigg and Goldsmith, 1976).

A biphasic effect on the ventilatory response to carbon dioxide was found by Becker and others (1976) with the second phase occurring 160 min after the last dose. Secretion of the drug into the stomach with subsequent jejunal reabsorption was suggested as a cause. However, Gorozeniuk, Whitwam and Morgan (1977) found fentanyl to be a suitable addition to methohexitone for short surgical procedures in unpremedicated patients and found no instances of respiratory depression after operation. Of the three patients with respiratory depression reported by Adams and Pybus (1978), occurring 4 h, 3 h and 30 min after the last dose of fentanyl, all had received papaveretum as premedication and two of the three had possible upper airway obstruction.

Therefore, fentanyl seemed a safe agent to use for outpatients and we found that it decreased the frequency of abdominal pain and backache on the day of operation. At the same time it did not compromise the surgical conditions nor increase the frequency of other postoperative sequelae such as nausea, vomiting, dizziness and drowsiness.

We conclude that fentanyl is a suitable agent for outpatient gynaecological surgery, in that it does afford some analgesia after operation, without increasing post-anaesthetic morbidity.

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MORBIDITE AU COURS DES INTERVENTIONS CHIRURGICALES GYNECOLOGIQUES SUR DES PATIENTES DE CONSULTATION EXTERNE

Comparaison de deux techniques d'anesthésie

RESUME

On a étudié l'efficacité du fentanyl, administré en tant que partie de la technique d'anesthésie, pour diminuer les douleurs abdominales après intervention chirurgicale gynécologique sur des patientes de consultation externe. Il a été trouvé que ce produit diminuait d'une manière significative la fréquence de la douleur abdominale au cours de la période allant du moment ou la patiente quitte l'hôpital à la première soirée, tout en ne compromettant pas les conditions chirurgicales et en n'augmentant pas la fréquence des autres séquelles postopératoires, comme par exemple les nausées et les vomissements.

STERBLICHKEIT BEI AMBULANTEN GYNÄKOLOGISCHEN OPERATIONEN

Ein vergleich von zwei narkosemethoden

ZUSAMMENFASSUNG

Die Wirksamkeit von Fentanyl, das als Teil einer Narkosetechnik verabreicht wird, um Unterleibsschmerzen nach ambulanten chirurgischen Eingriffen zu verringern, wurde untersucht. Die Haufigkeit solcher Schmerzen wurde durch Fentanyl in der Periode von der Entlassung bis zum ersten Abend wesentlich verringert, ohne die Operationsbedingungen schädlich zu beeinflussen oder die anderen postoperativen Erscheinungen wie Übelkeit und Erbrechen zu erhöhen.

MORBOSIDAD EN CIRUJIA GINECOLOGICA DE CONSULTORIO

Una comparación entre dos técnicas de anestesia

SUMARIO

Se examinó la eficacia del fentanilo, como parte de la técnica de anestesia para reducir el dolor abdominal después de una operación ginecológica en un paciente de consultorio. Se comprobó que reducía de manera significativa la frecuencia de los dolores abdominales durante el período que transcurría entre la dada de alta y la primera velada, mientras no comprometía las condiciones quirúrgicas ni tampoco aumentaba la frecuencia de otras secuelas postoperatorias, tales como náuseas y vómitos.

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NON-DEPOLARIZING NEUROMUSCULAR BLOCKERS AND THE EYE: A STUDY OF INTRAOCULAR PRESSURE

Pancuronium versus alcuronium

R. GEORGE, A. NURSINGH, J. W. DOWNING AND N. H. WELSH

SUMMARY

Intraocular pressure remained stable when either pancuronium or alcuronium was used to produce muscle relaxation, suggesting that alcuronium may be a reasonable alternative to pancuronium for routine surgery of the open eye, particularly in elderly patients with limited cardiac reserve.

Premedicant drugs, inhalation anaesthetic agents, systemic arterial and central venous pressure, and arterial oxygen and carbon dioxide tension are known to influence intraocular pressure (i.o.p.) (Duncalf, 1975). Al Abrak and Samuel (1974a) devised a study to minimize the effects of these factors, and compared the i.o.p. changes produced by pancuronium and tubocurarine during nitrous oxide in oxygen anaesthesia (Al Abrak and Samuel, 1974b). Although there was a significant reduction in i.o.p. following the administration of tubocurarine, there was no change with pancuronium.

Alcuronium has been the non-depolarizing muscle relaxant of choice for ophthalmic anaesthesia in our department for several years. The present study compares the effects of pancuronium and alcuronium on i.o.p. The technique of the study is similar to our previous investigation of i.o.p. changes during halothane and enflurane anaesthesia (Runciman et al., 1978) and is based upon that by Al Abrak and Samuel (1974a).

PATIENTS AND METHODS

Informed consent was obtained from 20 healthy, male patients (aged 16–43 yr) requiring surgical treatment for ophthalmic trauma. Ophthalmic abnormalities of the non-traumatized eye excluded the patient from the study. None of the surgical procedures was performed as an emergency, and the patients were in a state of normal hydration. Twelve patients required enucleation, four evisceration of a severely damaged eye, and the remaining four extensive repair to severe eyelid lacerations.

Premedication comprised morphine 10–15 mg i.m. and diazepam 5 mg i.m., 1 h before surgery. In the operating theatre a basal i.o.p. reading was obtained in the normal eye after instillation of a local anaesthetic solution to the conjunctival sac. All i.o.p. measurements were made using a Perkins hand-held applanation tonometer (Perkins, 1965). Measurements of systolic arterial pressure (Riva Rocci method) and heart rate (Mennen–Greatbatch Portoscope) were also obtained before induction of anaesthesia.

Further sedation was produced with droperidol 5 mg i.v. and fentanyl 100–200 μg i.v. After a suitable period of time to allow the sedation to take effect, the oropharynx and laryngeal inlet were sprayed with 2–4 ml of 4% lignocaine solution under direct laryngoscopy. Anaesthesia of the trachea was produced by the direct injection of 2 ml of 4% lignocaine solution through the cricothyroid membrane.

After 5 min of pre-oxygenation via a non-rebreathing anaesthetic circuit, anaesthesia was induced with 2.5% thiopentone 4.5–5.5 mg kg^{-1}. The trachea was intubated with a cuffed endotracheal tube and ventilation controlled using a Manley ventilator delivering a minute volume of 120 ml kg^{-1} min. The fractional inspired oxygen concentration ($F_{I_{O_2}}$) was maintained at a constant value of 0.4 by monitoring fresh gas flow with a Beckman OM.11 oxygen analyser, and adjusting the flow rates of oxygen and nitrous oxide appropriately. The fractional end-expired carbon dioxide concentration ($F_{E'_{CO_2}}$) was monitored continuously using a Beckman LB2 Infrared CO_2 analyser and maintained at approximately 0.05 by the addition of carbon dioxide to the fresh gas supply and adjusting the flow rates of oxygen

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and nitrous oxide appropriately in order to maintain $P\text{A}_{\text{O}_2}$ steady.

A 16-French gauge i.v. catheter was inserted into the right internal jugular vein for the measurement of central venous pressure (c.v.p.) with a saline manometer. The zero reference point was taken as the surface of the operating table and all measurements were made with the patient in the horizontal position.

Heart rate (photoelectric finger transducer) and e.c.g. were monitored continuously using a Mennen-Greatbatch Portoscope. Systolic arterial pressure was measured using a sphygmomanometer.

Measurements of i.o.p., systolic arterial pressure, heart rate and central venous pressure were made at 10, 15 and 20 min after induction of anaesthesia, by which time all the patients were in a stable state. A non-depolarizing muscle relaxant, either pancuronium 0.1 mg kg^{-1} or alcuronium 0.25 mg kg^{-1}, was administered i.v. on a random basis, 10 patients receiving each drug. The measurements were repeated at 5, 10 and 15 min following injection of the drug and surgery was then commenced. At the conclusion of the operation, residual neuromuscular blockade was antagonized with neostigmine 3.75 mg and atropine 1.2 mg i.v.

Data were analysed using Student's t test for the significance of the difference between two sample means, computed on a Hewlett-Packard 9815A desktop calculator. Comparisons were made between measurements obtained before induction and those at 20 min after anaesthesia commenced, and again between the latter measurements and those obtained 15 min after injection of the muscle relaxant.

RESULTS

The mean age of patients given pancuronium was significantly greater than that of those receiving alcuronium (31.4 yr ± SEM 2.2 *v.* 24.5 ± 1.9 yr; $P < 0.05$). The mean body mass of the two groups was similar (64.1 ± 3.2 *v.* 60.1 ± 2.7 kg). The difference in age was considered unimportant in view of the healthy physical status of the subjects studied, together with the fact that each patient acted as his own control.

Mean i.o.p. decreased in both groups of patients 20 min after induction of anaesthesia in comparison with awake control values, but this was only significant in the pancuronium group (fig. 1). Further reductions in i.o.p. following i.v. injection of both the muscle relaxants were statistically insignificant.

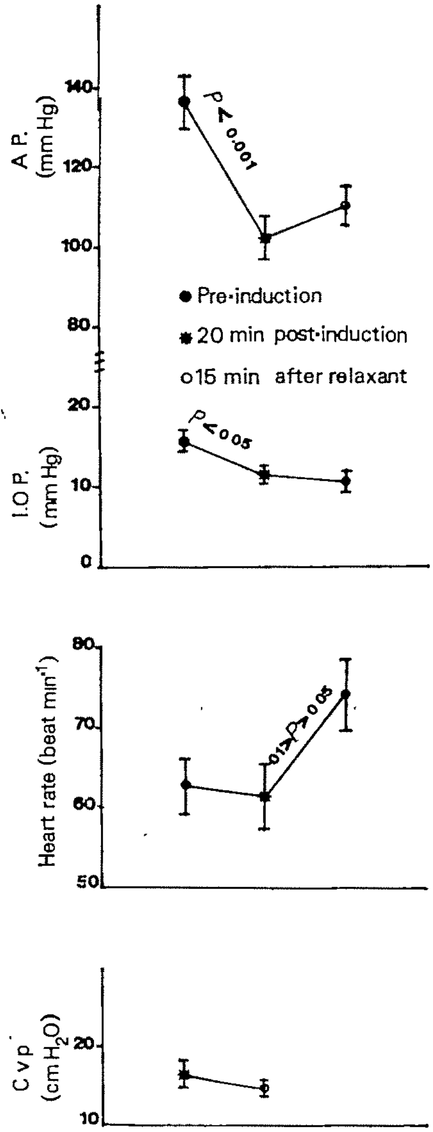

FIG. 1. Changes in arterial pressure (AP), intraocular pressure (i.o.p.), heart rate and central venous pressure (c.v.p.) before and after the i.v. administration of pancuronium 0.1 mg kg^{-1} (mean values: vertical bar = 1 SEM).

Mean systolic arterial pressure 20 min after anaesthesia commenced was significantly reduced in both groups of patients compared with control (pre-induction) values ($P < 0.001$). No further change occurred in either group thereafter (figs 1, 2).

In the alcuronium group there were no significant changes in heart rate throughout the study (fig. 2). However, heart rate increased following the i.v. injection of pancuronium (fig. 1), but this was not statistically significant ($0.1 > P > 0.05$). Mean c.v.p.

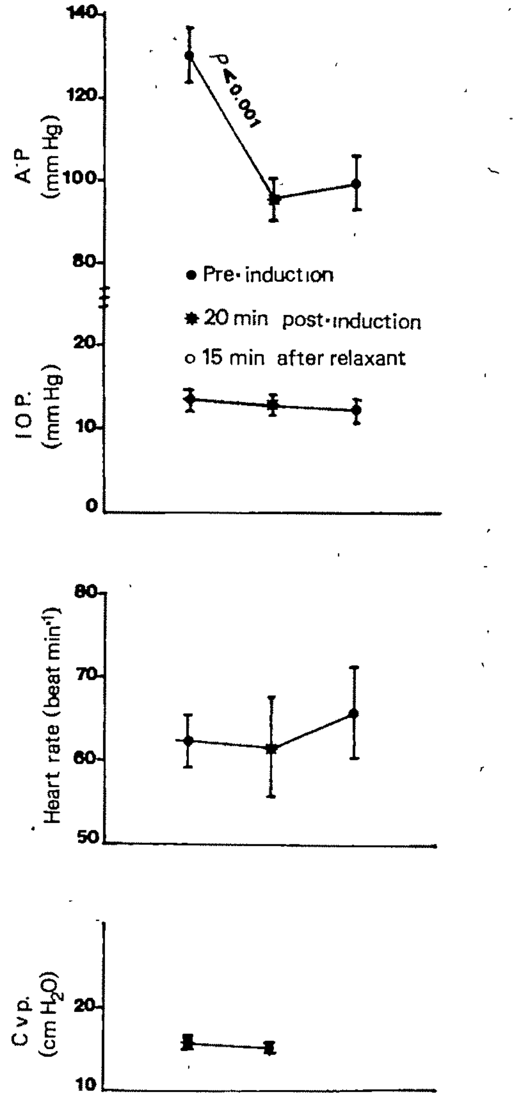

FIG. 2. Changes in arterial pressure (AP), intraocular pressure (i.o.p.), heart rate and central venous pressure (c.v.p.) before and after the i.v. administration of alcuronium 0.25 mg kg^{-1}.

during anaesthesia did not change following injection of either pancuronium or alcuronium. FE'_{CO_2} was maintained steady in both groups during the period of study (fig. 3).

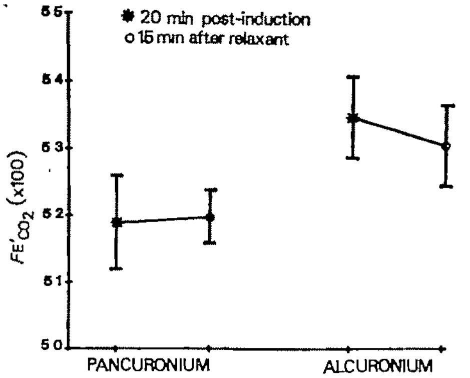

FIG. 3. End-expired carbon dioxide concentration (FE'_{CO_2}) before and after the i.v. administration of pancuronium and alcuronium.

DISCUSSION

Any increase in ocular vascular congestion during intraocular surgery is undesirable and possibly dangerous, and should be avoided in order to safeguard against the expulsion of vitreous humor from the open eye. Furthermore, it is desirable to achieve a normal or reduced i.o.p. before the eye is opened, to avoid expulsive haemorrhage and ocular disruption at the time of the incision (Duncalf, 1975). Therefore, the ideal anaesthetic technique for intraocular procedures should produce a moderate reduction in i.o.p., or maintain i.o.p. at near normal values, and avoid marked fluctuations during surgery.

The use of a non-depolarizing muscle relaxant allows controlled ventilation with nitrous oxide and oxygen, and this technique tends to maintain a stable intraocular pressure. Pancuronium has been suggested as the relaxant of choice for ophthalmic surgery since it produces little change in i.o.p. (Al Abrak and Samuel, 1974b). In contrast, tubocurarine appeared to produce a marked reduction in i.o.p. in association with significant alterations in cardiovascular haemodynamics.

Alcuronium has been used in our department for several years as the non-depolarizing muscle relaxant of choice. Kalff and Linzen (1969) have shown that alcuronium causes no change in i.o.p. unless the dose is sufficient to produce a concurrent decrease in systolic arterial pressure. Alcuronium, similar to tubocurarine, but not pancuronium, may reduce mean systemic vascular resistance and hence arterial pressure (Coleman et al., 1972). An excessive reduction in arterial pressure would be undesirable in the elderly patient undergoing ophthalmic surgery. However, a moderate decrease in the afterload of the heart, induced by anaesthesia, may be beneficial to the patient with reduced myocardial reserve. In contrast, pancuronium tends to increase the work load of the heart, by increasing heart rate, arterial pressure and cardiac output (Coleman et al., 1972).

In the present study, conducted under standardized conditions of anaesthesia, arterial and central venous pressure and $F\text{E}'_{\text{CO}_2}$, alcuronium produced no change in mean i.o.p., heart rate or arterial pressure—findings similar to those documented by Kalff and Linzen (1969). Similar circumstances prevailed after the administration of pancuronium, with regard to the average i.o.p., heart rate and arterial pressure. The latter results are in accord with those of Al Abrak and Samuel (1974b).

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This study was approved by the Ethical Committee of the Faculty of Medicine, University of Natal and Director of Hospital Services, Natal Provincial Administration.

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AGENTS DE BLOCAGE NEUROMUSCULAIRE NON DEPOLARISANT ET L'ŒIL: ETUDE DE LA PRESSION INTRAOCULAIRE

Pancuronium par rapport à alcuronium

RESUME

Lorsqu'on a utilisé le pancuronium ou l'alcuronium pour produire une relaxation du muscle, la pression intraoculaire est restée stable, ce qui laisse penser que l'alcuronium peut être une alternative raisonnable au pancuronium pour les interventions chirurgicales à l'œil ouvert, surtout chez les personnes âgées ayant une réserve cardiaque limitée.

NICHT-DEPOLARISIERENDE BLOCKIERUNGSMITTEL UND DAS AUGE: EINE STUDIE INTRAOKULAREN DRUCKES:

Pancuronium gegenuber alcuronium

ZUSAMMENFASSUNG

Intraokularer Druck blieb stabil, wenn entweder Pancuronium oder Alcuronium zur Muskelentspannung verwendet wurden—ein Hinweis dafur, dass Alcuronium eine brauchbare Alternative zu Pancuronium darstellen könnte, was Routineoperationen im offenen Auge betrifft, besonders bei älteren Patienten mit beschrankten kardialen Reserven.

BLOQUEADORES NEUROMUSCULARES NO DEPOLARIZANTES Y EL OJO: UN ESTUDIO DE PRESION INTRAOCULAR

Pancuronio versus alcuronio

SUMARIO

La presión intraocular permaneció estable cuando se empleó ya sea pancuronio o alcuronia para producir relajación muscular, lo que sugiere que el alcuronio podría ser una alternativa razonable al pancuronio para circugía de rutina del ojo abierto, especialmente en pacientes de edad avanzada con reserva cardíaca limitada.

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PROGRAMMABLE CALCULATOR: A PROGRAM FOR USE IN THE INTENSIVE CARE UNIT

G. N. C. Kenny

SUMMARY

A program has been prepared for use in a small programmable calculator to allow the rapid and accurate determination of derived data. Changes in oxygen availability, deadspace and shunt fraction can be obtained in a few seconds and therapy altered accordingly. FI_{O_2} required to produce a desired Pa_{O_2} can be obtained using the iso-shunt concept.

The introduction of pocket-sized programmable calculators has allowed complex calculations to be made rapidly and accurately at the bedside. In this way, information obtained from monitoring systems can be computed and used to determine immediate alterations in therapy. For example, obtaining the shunt fraction with a standard calculator would be tedious and time-consuming, but with a programmable calculator the data obtained from the patient is merely entered and the calculations are performed automatically.

The attainment of the best positive end-expiratory pressure (PEEP) for any patient is a further example of the use of the calculator in the intensive care unit. The most suitable PEEP can be found by calculating the oxygen availability for the patient at different values of PEEP (Suter, Fairley and Isenberg, 1975). The oxygen availability is obtained from the product of the arterial oxygen content and the cardiac output. These calculations can be computed within a few seconds of entering the Pa_{O_2}, haemoglobin concentration and cardiac output, thus allowing rapid adjustment of PEEP to the optimum value.

The Texas TI59 calculator has been available in the U.K. for several months and costs about £160. It has a storage capacity of 479 program steps with 59 spaces available for storage of data, but this can be rearranged to give from 960 program steps and no data registers to 160 program steps with 100 data stores as required. The calculator has a rechargeable battery pack which gives 2–3 h of continuous use when fully charged.

The programs are recorded on small magnetic cards (7.5 mm × 1.5 mm) which are entered into a slot in the calculator and pulled through by an integral drive motor. Data to be entered are typed into the display and entered into the specific part of the program by pressing the appropriate key. One further advantage of this particular model is the availability of modules which fit into the back of the calculator. A statistics module is available which allows *t* values, *P* values, mean, standard deviations and standard errors to be calculated in a few seconds.

Program design

Data entered as shown in table I allow the calculation of the values shown outlined by dotted lines in table I.

A program has been prepared to calculate the values shown in table I. While designed and entered as a complete unit, the program has the advantage that it can be run in separate sections depending on the patient information available.

V_D/V_T

The ratio of deadspace to tidal volume is calculated from Pa_{CO_2} and $P\bar{E}_{CO_2}$ using the formula:

$$V_D/V_T = \frac{Pa_{CO_2} - P\bar{E}_{CO_2}}{Pa_{CO_2}}$$

Ca_{O_2}

Entry of pH and Pa_{CO_2} before Pa_{O_2} allows the correction of P_{O_2} using the formula (Astrup et al., 1965):

$$Pa_{O_2corr} = Pa_{O_2} \times 10^{0.48\,(\mathrm{pH}-7.4)+0.06\,(\log 5.32-\log Pa_{CO_2})}$$

Temperature correction is performed for all blood-gas values by the Radiometer ABL2 blood-gas analyser used in our intensive care unit, but could be included in the program if required.

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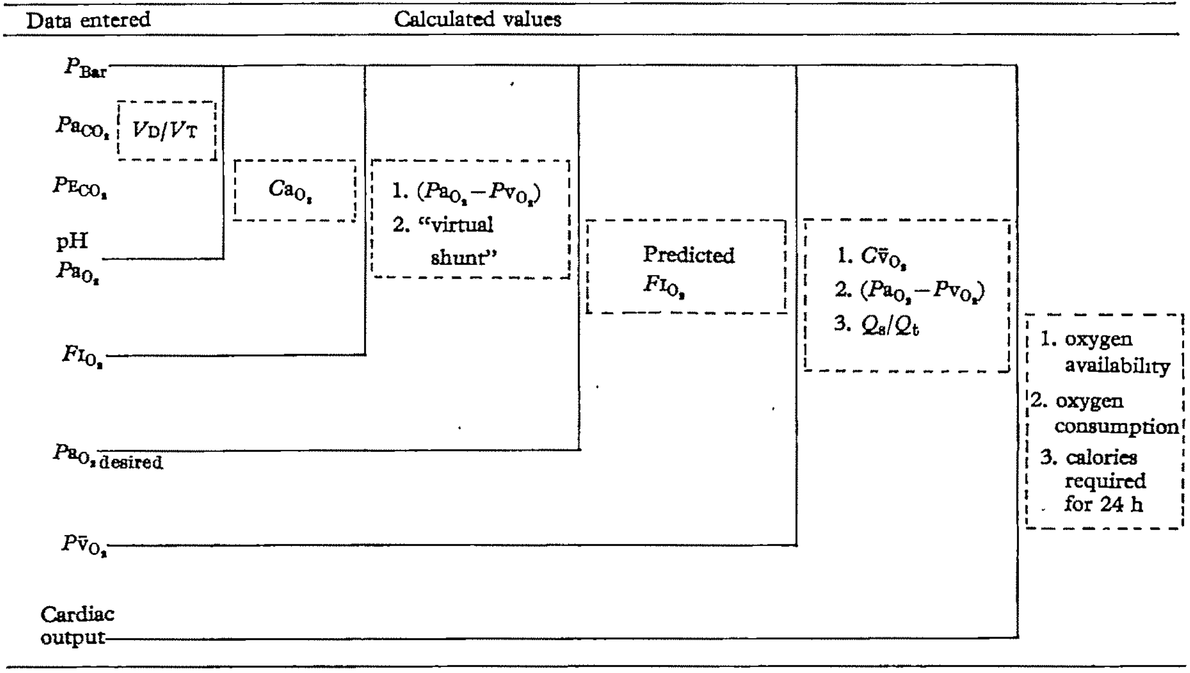
TABLE I. *Data which are entered and the values which can be calculated, using the programmable calculator*



The haemoglobin saturation is obtained by substituting the corrected Pa_{O_2} value in the Kelman equation as modified by Thomas (Kelman, 1966; Thomas, 1972):

$$\text{Saturation} = \frac{n^4+An^3+Bn^2+Cn}{n^4+An^3+Dn^2+En+F}$$

where $n = Pa_{O_2\text{corr}}$; $A = 15$; $B = 2.045\times10^3$; $C = -2\times10^3$; $D = 2.4\times10^3$; $E = 3.11\times10^4$; $F = 2.4\times10^6$.

Using this algorithm, any deviation of saturation from the standard Severinghaus oxyhaemoglobin dissociation curve is less than 1% (Severinghaus, 1966).

Haemoglobin concentration (g dl^{-1}) is entered in the final calculation to obtain the arterial oxygen content. The oxygen combining factor for haemoglobin is taken as 0.06 (Foëx et al., 1970).

$$Ca_{O_2} = \text{saturation}\times\text{Hb (g dl}^{-1})\times0.06 + (0.01\ \text{mmol litre}^{-1}\times Pa_{O_2\text{corr}})$$

The calculation of the oxygen content of a blood sample from the oxygen tension is used repeatedly in the program, and it is written as a separate "O_2 content subroutine".

$(PA_{O_2}-Pa_{O_2})$*; "virtual shunt"*

$(PA_{O_2}-Pa_{O_2})$ can be used as an estimate of the degree of pulmonary dysfunction, and it has been recommended that the value must be less than 39.9–59.9 kPa before a patient is liable to be successfully weaned from a ventilator (Feeley and Hedley-Whyte, 1975). Entry of the barometric pressure and FI_{O_2} allows the calculation of PA_{O_2} from the conventional alveolar air equation:

$$PA_{O_2} = (P_{Bar}-47)\,FI_{O_2}-PA_{CO_2}\left(FI_{O_2}+\frac{1-FI_{O_2}}{0.8}\right)$$

However, this assumes that the patient is in a steady state and that the oxygen concentration and the inert gas content of the inspired mixture have not been altered recently.

Where these conditions are not fulfilled an inaccurate assessment of the PA_{O_2} will be obtained using the standard equation. If the mixed expired gas can be sampled, an alternative form of the equation may be used (Filley, MacIntosh and Wright, 1954; Nunn, 1963):

$$PA_{O_2} = (P_{Bar}-47)\,FI_{O_2}-PA_{CO_2}\left(\frac{PI_{O_2}-P\bar{E}_{O_2}}{P\bar{E}_{CO_2}}\right)$$

No assumption is made in this equation that the inert gases present in the lungs are in equilibrium with those in the inspired mixture. This form of the equation can therefore be used either during anaesthesia or during the subsequent period of elimination of the anaesthetic.

The value for $(PA_{O_2} - Pa_{O_2})$ is displayed, and the program can be halted at this point or can be allowed to continue, in which case the "virtual shunt" is calculated and displayed (Benatar, Hewlett and Nunn, 1973). This assumes $(Pa_{O_2} - Pv_{O_2})$ of 5 ml dl^{-1} blood and calculates the shunt fraction using the formula:

$$\frac{\dot{Q}_s}{\dot{Q}_t} = \frac{Cc'_{O_2} - Ca_{O_2}}{Cc'_{O_2} - [Ca_{O_2} - (Pa_{O_2} - Pv_{O_2})]}$$

$Pa_{O_2,\mathrm{desired}}$

If the arterial Po_2 is not acceptable, FI_{O_2} which is required to achieve an acceptable Pa_{O_2} can be obtained using the iso-shunt concept. The formula used to calculate the "virtual shunt" can be rearranged to give:

$$Cc'_{O_2} - Ca_{O_2} = \frac{(\dot{Q}_s/\dot{Q}_t)(Pa_{O_2} - Pv_{O_2})}{1 - \dot{Q}_s/\dot{Q}_t}$$

If it is assumed that changing FI_{O_2} will not change the value:

$$\frac{(\dot{Q}_s/\dot{Q}_t)(Pa_{O_2} - Pv_{O_2})}{1 - \dot{Q}_s/\dot{Q}_t}$$

then $(Cc'_{O_2} - Ca_{O_2})_{\mathrm{old}} = (Cc'_{O_2} - Ca_{O_2})_{\mathrm{new}}$ and $Cc'_{O_2\mathrm{new}} = Cc'_{O_2\mathrm{old}} - Ca_{O_2\mathrm{old}} + Ca_{O_2\mathrm{new}}$.

Entry into the program of $Pa_{O_2\mathrm{new}}$, which it is wished to achieve, allows calculation, using the oxygen content subroutine described earlier, of $Cc'_{O_2\mathrm{new}}$. The values for $Cc'_{O_2\mathrm{old}}$ and $Ca_{O_2\mathrm{old}}$ have already been obtained from previous calculations and are held in data stores.

It is not possible to derive Pc'_{O_2} directly from Cc'_{O_2}, and a "trial and error" or iterative method has to be used to obtain a Po_2 which, when entered into the oxygen content subroutine, yields a value for oxygen content which is acceptably close to the $Cc'_{O_2\mathrm{new}}$ being sought.

When the oxygen content obtained using the test Po_2 varies by less than 0.02 ml dl^{-1} of blood from the required Cc'_{O_2}, the test Po_2 is accepted and FI_{O_2} calculated from that value using the standard alveolar air equation, since it is assumed that the patient will be in a steady state before any alteration in ventilation is considered:

$$FI_{O_2} = \frac{PA_{O_2} - (Pa_{CO_2}/0.8)}{P_{\mathrm{Bar}} - 47 - Pa_{CO_2} - (Pa_{CO_2}/0.8)}$$

$\dot{Q}_s/\dot{Q}_t$; $(Pa_{O_2} - Pv_{O_2})$

If P_{O_2} of a mixed venous sample is entered to the program, $C\bar{v}_{O_2}$ is displayed. The true shunt fraction is calculated and displayed when FI_{O_2} is entered. The program then displays $(Pa_{O_2} - Pv_{O_2})$.

Oxygen availability; oxygen consumption per min; calories required for 24 h

Entry of cardiac output (litre min^{-1}) allows the calculation of the oxygen availability (ml min^{-1}), and this can be compared with the calculated oxygen consumption. The energy output for a patient at rest oxidizing an "average" diet is 4.83 Cal for every litre of oxygen consumed. The energy–oxygen ratios for the different categories of food do not differ greatly from this value: carbohydrates are within +5%, proteins within −8%, lipids within −2% and ethanol within +1% of the figure (Brown and Brengelman, 1965). Calculating the appropriate oxygen consumption in litre per day allows the energy output per day for that patient to be derived and the caloric intake to be matched accordingly.

The program has been used to monitor the changes in shunt fraction, oxygen availability and oxygen consumption in a number of patients in the intensive care unit, from arterial samples and from mixed venous samples and cardiac output measurements obtained using triple lumen thermodilution catheters. This has allowed the rapid adjustment of PEEP to provide the optimum value for the individual patient by monitoring the changes in oxygen availability. Suter, Fairley and Isenberg (1975) showed that, in normovolaemic patients, the optimum value for PEEP as determined by the oxygen availability for the patient, was correlated with $P\bar{v}_{O_2}$. However, variations in arterio–venous shunting or alterations in the peripheral circulation could alter $P\bar{v}_{O_2}$ and possibly provide an inaccurate assessment of the optimum PEEP. The use of the programmable calculator allows easy and rapid measurement of the oxygen availability which reflects more directly the benefits and disadvantages of PEEP on the cardiovascular system. The values of PEEP required have varied from 5 to 15 cm H_2O and could not have been obtained so simply without the use of the programmable calculator. The use of the iso-shunt concept to predict FI_{O_2} required to obtain a desired Pa_{O_2} has been shown to be reasonably accurate in the majority of patients (Benatar, Hewlett and Nunn, 1973; Lawler and Hewlett, 1978). This part of the program can be used with knowledge only of the FI_{O_2} and arterial blood-gas tensions.

The program has also been used for teaching to demonstrate the effects of changes in cardiac output, haemoglobin concentration and arterial PO_2 in determining the delivery of oxygen to a patient.

Entry of the program uses nearly all the available stores in the calculator memory, and so more complex programs cannot be run on this machine. Also, the speed of calculation is relatively slow compared with larger, desk-top machines. This only becomes troublesome when iterative loops are run as, for example, when predicting FI_{O_2} required to obtain a specified Pa_{O_2}. However, taking into consideration the relatively low cost and the portability of the calculator, it would appear to justify a place in the intensive care unit, especially if no other computational facilities are available.

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CALCULATEUR PROGRAMMABLE: PROGRAMME A UTILISER DANS LES CENTRES DE REANIMATION

RESUME

On a préparé un programme à utiliser dans un petit calculateur programmable afin de pouvoir interpréter rapidement et avec précision les données qui en découlent. On peut obtenir en quelques secondes une indication des changements dans la disponibilité en oxygène, l'espace mort et la fraction de dérivation, et modifier de ce fait le traitement. On peut obtenir la FI_{O_2} nécessaire pour produire la Pa_{O_2} désirée, en utilisant le concept isoshunt.

PROGRAMMIERBARER KALKULATOR: EIN PROGRAMM ZUR VERWENDUNG IN INTENSIVPFLEGEABTEILUNGEN

ZUSAMMENFASSUNG

Ein Programm fur einen kleinen, progammierbaren Kalkulator wurde verfasst, um die schnelle und genaue Bestimmung abgeleiteter Daten zu ermoglichen. Veránderungen in der Sauerstoffverfugbarkeit, Totraum und Verschieberfraktion konnen in wenigen Sekunden ermittelt, und die Therapie entsprechend verandert werden. FI_{O_2}, das zur Erzielung der gewunschten Pa_{O_2} erforderlich ist, kann unter Verwendung des Iso-Verschieb-Konzepts erzielt werden.

CALCULADORA PROGRAMABLE: UN PROGRAMA PARA USO EN LA UNIDAD DE TRATAMIENTO INTENSIVO

SUMARIO

Se elaboró un programa para uso en una calculadora programable pequeña que permite determinar rápida y exactamente los datos derivados. En pocos segundos, es posible lograr los cambios en la disponibilidad de oxígeno, los puntos muertos y la fracción de derivación y, conforme, modificar la terapia. Puede obtenerse el FI_{O_2} necesario para producir un Pa_{O_2} deseado, al usar el concepto de iso-derivación.

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COMPARISON OF ANTI-POLLUTION MODIFICATIONS OF MAPLESON A AND D ANAESTHETIC SYSTEMS

P. K. ANDERSEN AND P. HOLE

SUMMARY

Hafnia A and Hafnia D anaesthetic systems are non-polluting modifications of the Mapleson A and D systems. The excess gas is vented in the Hafnia systems directly and continuously via a calibrated ejector flowmeter. Sixteen adult patients anaesthetized for abdominal surgery were ventilated with either Hafnia A or D systems at six different fresh gas flows. No difference between the Hafnia A and D systems could be demonstrated in the values of arterial carbon dioxide tension measured with the same fresh gas flow, despite gas flows in opposite directions.

The Hafnia A and Hafnia D anaesthetic breathing systems are non-polluting modifications of the Mapleson A and D types (Christensen et al., 1978). The excess gas is not vented through the expiratory valve in the Hafnia systems, but removed directly and continuously via a calibrated ejector flowmeter (Jørgensen, 1974). These systems are in balance, provided the excess gas removal is equal to the fresh gas inflow. Both systems may be employed for both spontaneous and controlled ventilation. In contrast to the Mapleson A system, however, the fresh gas requirements of the Hafnia A version are the same for both spontaneous and controlled ventilation (Sykes, 1968; Thomsen and Jørgensen, 1976).

In the Mapleson systems, it has been demonstrated that there is less rebreathing in the D system than in the A system during controlled ventilation (Waters and Mapleson, 1961). Corresponding information is not available for the Hafnia A and Hafnia D systems.

The object of the present investigation of the Hafnia A and D systems was to compare the extent of rebreathing in the two systems (expressed as an increase in the arterial carbon dioxide tension), during decreasing fresh gas flows ($\dot{V}_f$) and under controlled normoventilation.

MATERIALS AND METHODS

The study was performed on 16 adult patients undergoing abdominal surgery. The patients were healthy and free from cardiovascular or pulmonary disease. Premedication comprised atropine 0.4–0.5 mg and pethidine 50–75 mg i.m. 1 h before induction of anaesthesia. Anaesthesia was induced and maintained with droperidol, fentanyl and nitrous oxide 50–67% in oxygen. Pancuronium was used for neuromuscular blockade and a cuffed endotracheal tube was inserted into the trachea. In eight patients, the lungs were ventilated using the Hafnia A system (A system) and in the remaining eight ventilation was with a Hafnia D system (D system). In the A system (fig. 1), the fresh gas was introduced through a T-tube at the reservoir bag, and excess gas was removed via a calibrated ejector flowmeter at the patient connection. The corrugated tube, inserted between the inlet and outlet for gases, had a volume of approximately 500 ml (fig. 1). In the D system (fig. 1), the introduction and removal of the gas took place in the reverse order. The rate of excess gas evacuation was equilibrated with the inflow of fresh gas when the systems were in use. A Beaver Ventilator was connected to the

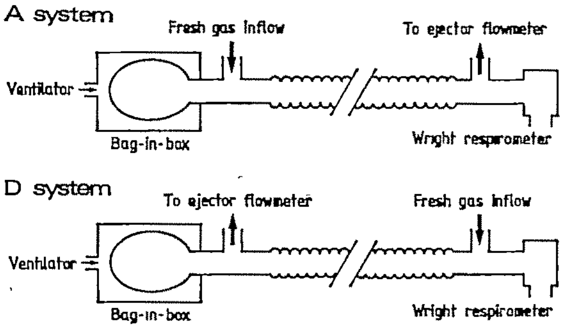

FIG. 1. Diagram of the modifications to the Mapleson A (A system) and Mapleson D (D system) anaesthetic systems. Both systems are connected to a Beaver Ventilator via a "bag-in-box".

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systems at the site of the reservoir bag, the latter being replaced by a bag-in-box.

Normal ventilation for each patient was calculated according to the Radford Nomogram (Radford, 1955), without correction for endotracheal intubation. The respiratory frequency was 10 b.p.m. and the inspiratory–expiratory ratio 1 : 2. The expired minute volume was checked during the investigation with a Wright respirometer (fig. 1).

Six different fresh gas flows were used for each patient, each a multiple of the normal ventilation. The following multiples were employed for the calculations, in the order shown: 2—1.5—1.25—1—0.75—0.5. The fresh gas flows were adjusted to the nearest 100 ml using the same flowmeters of an anaesthetic machine.

After 20 min of ventilation at each fresh gas flow, an arterial blood sample was withdrawn into a heparinized 2-ml syringe via a cannula introduced into the radial artery. These blood samples were analysed immediately (Acid–Base Laboratory I, Radiometer, Copenhagen) for $P\text{CO}_2$, $P\text{O}_2$ and pH.

The fresh gas flows were calculated as ml kg^{-1} min at ATPD. (Room temperature 20–22 °C.)

Student's *t* test was employed for statistical comparison. A significance level of $2P < 0.01$ was used.

RESULTS

The patients for whom the A system was used had a mean age of 67 yr (range 50–79 yr), and a mean weight of 68.4 kg (range 52–93 kg); with the D system the corresponding values were 70 yr (range 47–77 yr) and 68.8 kg (range 52–93 kg).

Values of Pa_{CO_2} and fresh gas flows are shown in table I. For each multiple of normoventilation, the fresh gas flows used were identical for the two systems (table I). There was no significant difference between the A and D systems with respect to the the Pa_{CO_2} values for the same fresh gas flow (fig. 2).

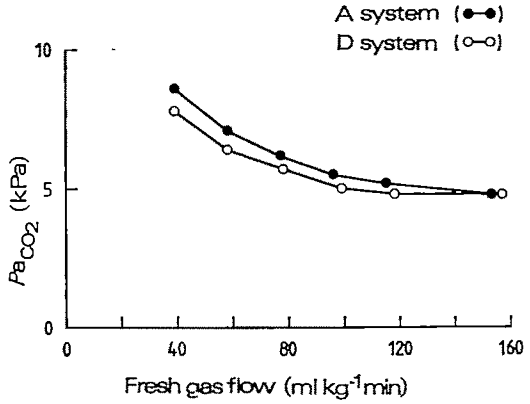

FIG. 2. Mean arterial carbon dioxide tension (Pa_{CO_2}) at six different fresh gas flows for A and D systems, respectively. There is no significant difference between Pa_{CO_2} values at the same fresh gas flows.

DISCUSSION

No difference was found between the Pa_{CO_2} values between the A and D systems with the same fresh gas flow during controlled normoventilation, taking a significance level of $2P < 0.01$.

With a step reduction in ventilation, Pa_{CO_2} does not reach a steady state before 70 min (Sullivan, Patterson and Papper, 1966). If this applies to a step reduction in fresh gas flow in a rebreathing circuit, only 60% of the total increase in Pa_{CO_2} will have occurred in 20 min. Individual Pa_{CO_2} values have therefore been utilized only for comparing the two systems at the same fresh gas flow. The curves shown in figure 2 cannot be used for the prediction of Pa_{CO_2}.

Thomsen and Jørgensen (1976) found that, with regard to the A system, rebreathing during controlled normoventilation according to the Radford nomogram started to occur when the fresh gas flow was reduced to 1.35 times the minute ventilation. It was demonstrated in the same investigation, with respect to the

TABLE I. *Pa_{CO_2} (kPa, mean ± SEM) at different fresh gas flows ($\dot{V}_f$) (ml kg^{-1} min, mean ± SEM) with a constant respiratory minute volume (normoventilation according to the Radford nomogram). The fresh gas flows are adjusted to ATPD*

Fresh gas flow (fraction of normoventilation)	A system ($n = 8$)		D system ($n = 8$)	
	$\dot{V}_f$	Pa_{CO_2}	$\dot{V}_f$	Pa_{CO_2}
2.0	153 ± 3.8	4.8 ± 0.17	157 ± 2.3	4.8 ± 0.10
1.5	115 ± 2.9	5.2 ± 0.11	118 ± 1.7	4.8 ± 0.11
1.25	96 ± 2.3	5.5 ± 0.16	99 ± 2.8	5.0 ± 0.15
1.0	77 ± 1.9	6.2 ± 0.14	78 ± 1.1	5.7 ± 0.23
0.75	58 ± 1.4	7.1 ± 0.22	58 ± 1.0	6.4 ± 0.38
0.5	39 ± 1.0	8.6 ± 0.29	39 ± 0.6	7.8 ± 0.61

A system, that there is no difference between the fresh gas requirements with both spontaneous and controlled ventilation. The same does not apply to the D system, in that the fresh gas requirements for this system are two to 2.5 times the basal minute ventilation with spontaneous ventilation (Christensen et al., 1978). From this it follows that the A system has the advantage over the D system that the fresh gas flow does not require adjustment when changing from controlled to spontaneous ventilation or *vice versa.* However, it is possible that other ventilatory patterns during controlled ventilation could result in different fresh gas requirements.

In spite of a different pattern of fresh gas flow no difference in effective function was detected between the Hafnia A and the Hafnia D systems during controlled normoventilation with the ventilatory pattern used in this study.

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COMPARAISON DES MODIFICATIONS ANTI-POLLUTION AUX SYSTEMES D'ANESTHESIE MAPLESON A ET D

RESUME

Les systèmes d'anesthésie Hafnia A et Hafnia D sont des modifications non polluantes des systèmes Mapleson A et D. Dans les systèmes Hafnia, l'excédent de gaz est ventilé directement et en continu par l'intermédiaire d'un débitmètre éjecteur étalonné. Seize patients adultes anesthésiés pour une intervention chirurgicale à l'abdomen ont été ventilés par les systèmes Hafnia A ou D à six débits différents de gaz frais. On n'a pu prouver aucune différence entre les systèmes Hafnia A et D dans les valeurs de la tension de l'acide carbonique artériel mesurée avec le même débit de gaz frais, en dépit des débits de gaz allant dans des directions opposées.

VERGLEICH VON VERUNREINIGUNGSSCHUTZ-MODIFIKATIONEN DER NARKOSESYSTEME MAPLESON A UND MAPLESON D

ZUSAMMENFASSUNG

Hafnia A- und Hafnia D-Narkosesysteme sind nichtverunreinigende Modifikationen der Mapleson A- und D-Systeme. Das uberschüssige Gas wird direkt und kontinuierlich über einen geeichten Durchflussmesser in die Hafnia-Systeme geleitet. Sechzehn erwachsene Patienten, narkotisiert für Unterleibseingriffe, wurden mit Hafnia A- oder D-Systemen mit sechs verschiedenen Frischgasstromen belüftet. Die Werte der arteriellen Kohlendioxydspannung, gemessen mit denselben Frischgasstromen, zeigten keine Unterschiede zwischen Hafnia A-und Hafnia D-Systemen, trotz Gasstromen in entgegengesetzten Richtungen.

COMPARACION ENTRE MODIFICACIONES ANTIPOLUCIONALES DE LOS SISTEMAS ANESTESICOS MAPLESON A Y D

SUMARIO

Los sistemas anestésicos Hafnia A y Hafnia D son modificaciones antipolucionales de los sistemas Mapleson A y D. El exceso de gas es purgado directa y continuamente en los sistemas Hafnia, por vía de un flujómetro eyector calibrado. Dieciseis pacientes adultos anestesiados para cirugía abdominal fueron ventilados con los sistemas Hafnia, ya sea A o D, a seis velocidades de circulación diferentes de gas fresco. No pudo demostrarse diferencia alguna entre los sistemas Hafnia A y D en los valores de tensión de dioxido de carbono, medidos con la misma circulación de gas fresco, a pesar de circulaciones de gas en sentidos contrarios.

Br. J. Anaesth. (1979), **51**, 801

HEPATITIS FOLLOWING THIOPENTONE

A case report

L. HASSELSTRØM AND M. B. KRISTOFFERSEN

SUMMARY

A patient developed pyrexia and jaundice following repeated anaesthesia. The evidence suggests that thiopentone was the causative agent. This incident emphasizes the need for caution in associating jaundice and hepatitis with halothane in patients who have received thiopentone and halothane.

In recent years many publications have described adverse reactions to anaesthetic agents. Although interest has centred largely on the hepatotoxicity of halothane, sensitivity reactions to induction agents such as Althesin have caused concern also. Thiopentone is associated with occasional hypersensitivity reactions which, although confined usually to the skin, sometimes consist of a true anaphylactoid response. Hepatotoxicity is not usually considered to be a complication of thiopentone administration (Dundee and Wyant, 1974; Dundee et al., 1974; Clarke et al., 1975; Baxter, 1977). However, the patient described in this paper developed pyrexia and jaundice following anaesthesia and the evidence pointed to thiopentone as the causative agent.

CASE REPORT

The patient was a healthy 29-yr-old woman with no previous history of atopy or allergy. She had been anaesthetized first in 1974 for Caesarean section. On that occasion anaesthesia was induced with thiopentone and maintained with nitrous oxide and an infusion of suxamethonium. Anaesthesia was uneventful but a troublesome wound infection developed after operation. Anaesthesia was required on a further five occasions over the next 20 days to allow drainage of an abscess and wound cleaning. The agents used are shown in the accompanying diagram (table I). On the last occasion both thiopentone and halothane were employed. Pyrexia (41.4 °C) developed soon after anaesthesia and was followed by jaundice which lasted for 10 days.

In 1975 (14 months later) the patient was admitted to hospital for termination of pregnancy. Anaesthesia was induced with thiopentone and maintained with nitrous oxide. Halothane was not used. Pyrexia (40.0 °C) developed after operation, and jaundice, which appeared on the following day, persisted for 2 days.

The patient was seen first in our department in December 1977 when she was again to be anaesthetized for evacuation of the products of conception. Premedication consisted of morphine 5 mg and hyoscine 0.2 mg. Anaesthesia was induced with atropine 0.6 mg and thiopentone 450 mg and maintained with nitrous oxide in oxygen in a ratio of 5 : 3 litre min^{-1}. A non-rebreathing system was used with new rubber throughout. Cervical dilatation and uterine curettage were performed. Surgery and anaesthesia were uneventful and the procedure lasted for 7 min. On the following day the patient's temperature was 39.4 °C and her liver function tests were abnormal (table II).

On the 3rd day after operation ectopic pregnancy was diagnosed and the patient was prepared for laparotomy. On this occasion premedication consisted of morphine 10 mg and hyoscine 0.4 mg. Anaesthesia was induced with a chlormethiazole infusion and maintained with nitrous oxide and oxygen in a ratio of 6 : 3 litre min^{-1}. Tubocurarine was administered to produce neuromuscular blockade and to facilitate intermittent positive pressure ventilation. Salpingo-oophorectomy and liver biopsy were performed; palpation of the liver and gall bladder revealed no abnormality.

After operation the patient remained apyrexial and the liver enzyme concentrations continued to decrease towards normal (fig. 1, table II).

Tests for hepatitis B antigen were negative as were those for porphyria.

The liver biopsy contained nine portal tracts; the lobular architecture was normal. There were no signs of collapse in the minor structural framework proved

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TABLE I. *Anaesthetic agents used on nine occasions. Reactions to these are shown in last two columns*

	Premedication	Induction	Maintenance	Other drugs	Post-op. pyrexia	Post-op jaundice
1974 Caesarean section	Pentobarbitone Aprobarbitone Pethidine	Thiopentone Suxamethonium	Nitrous oxide Suxamethonium	Hydrallazine Pethidine Diazepam	?	—
1974 Wound cleaning	Pentobarbitone Aprobarbitone Pethidine	Thiopentone	Nitrous oxide Halothane	Pethidine Diazepam	?	—
1974 Wound cleaning	Pentobarbitone Aprobarbitone Pethidine	Halothane	Nitrous oxide Halothane	Diazepam Pethidine	?	—
1974 Wound cleaning	Pentobarbitone Pethidine	Halothane	Nitrous oxide Halothane	Diazepam Furosemide	?	—
1974 Wound cleaning	Pentobarbitone Pethidine	Halothane	Nitrous oxide Halothane	Diazepam Furosemide	? ?	— —
1974 Wound cleaning	Pentobarbitone Aprobarbitone Pethidine	Thiopentone	Nitrous oxide Halothane	Diazepam	+ +	+ +
1975 Evacuation of uterus	Pentobarbitone Aprobarbitone Pethidine	Thiopentone	Nitrous oxide	Diazepam	+	+
1977 Evacuation of uterus	Morphine Hyoscine	Thiopentone	Nitrous oxide	—	+	+
1977 Laparotomy	Morphine Hyoscine	Chlormethiazole Tubocurarine	Nitrous oxide Tubocurarine	—	—	—

TABLE II. *Concentrations of liver enzymes plus bilirubin at various times (year, day and month), usually in connection with anaesthesia. Reference values at our laboratory are: serum bilirubin* < 1.3 *mg dl*$^{-1}$, *LDH* 100–400 *u. litre*$^{-1}$, *alkaline phosphatase* 80–220 *u. litre*$^{-1}$, *g.o.t.* < 40 *u. litre*$^{-1}$, *g.p.t.* < 35 *u. litre*$^{-1}$

	1974 30.6	5.7	8.7	10.7	1975 19.9	1976 8.7	1977 29.4	14.12	21.12	22.12	23.12	24.12	25.12	30.12	1978 2.1
Bilirubin (mg dl^{-1})	1.4	2.5	4.7	3.9	3.0	0.5	0.75	0.8	2.7	1.2	0.7	0.5	0.4	0.5	0.4
Alk. phos. (u. litre^{-1})			480	780		140	170	150	470	455	330	290	235	220	230
LDH (u. ml^{-1})						260		500	1410	750	620	475	440	470	415
G.p.t. (u. ml^{-1})			1260	700	340	15	20	30	600	440	275	170	90	55	40
G.o.t. (u. ml^{-1})	45		910	310				45	410	210	70	60	45	50	50

by the silver impregnation technique. Neither fibrosis nor cirrhosis was seen. In the parenchyma slight steatosis and a few focal areas of liver cell necroses were observed. The portal tracts contained few lymphocytes in the junction between the liver parenchyma and the connective tissue. There was a moderate oedema and a light degree of centrilobular cholestasis (figs 2A, B and C).

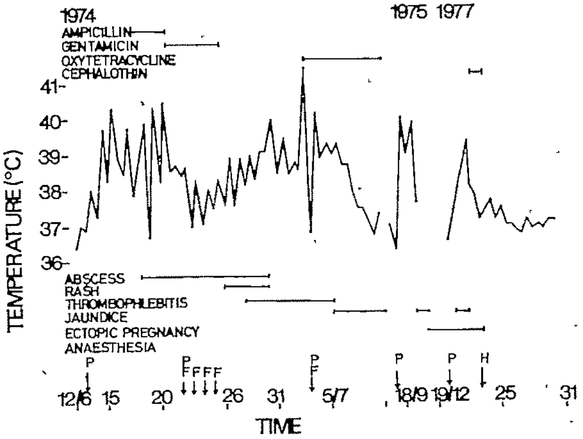

FIG. 1. Temperature–time chart covering three separate years. The administration of antibiotics and the complications are indicated by horizontal lines. Vertical arrows indicate anaesthesia, where P (thiopentone), F (halothane) and H (chlormethiazole (Heminevrin)), are main anaesthetic agents.

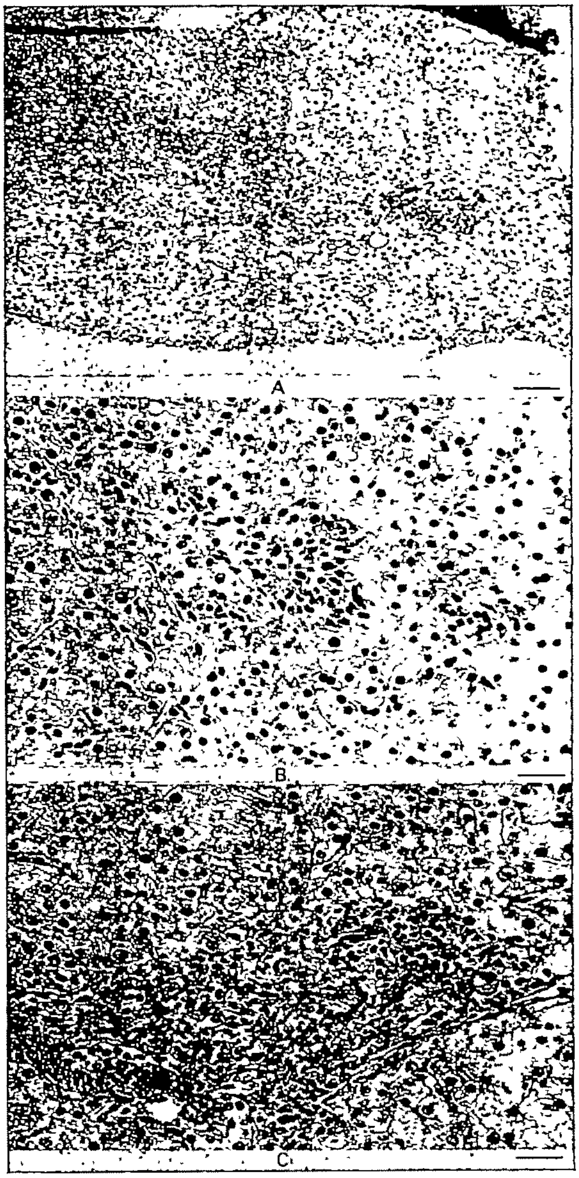

FIG. 2. A: Liver biopsy (bar = 0.2 mm). Small focal area of liver cell necrosis and a minor degree of steatosis are seen. B: Liver biopsy (bar = 0.025 mm). Focal necrosis and proliferation of Kupffer cells. C: Lymphocytic infiltration in the portal space and degenerations along the membrana limitans (bar = 0.025 mm).

DISCUSSION

A review of the literature reveals that barbiturates have, on occasion, been associated with liver toxicity. Pagliaro, Campesi and Aguglia (1969) reported a patient with generalized skin eruption, mucosal lesions and cholestatic jaundice following the oral administration of barbiturate. Hepatic impairment attributable to thiopentone was reported by Vaizey (1938). His patient, however, was severely anaemic, a factor which could increase the risk of liver impairment during anaesthesia. Dundee (1955) showed that doses of thiopentone exceeding 750 mg could induce liver dysfunction. Hart and Fitzgerald (1975) reported an incident of jaundice after surgery where halothane was not used and stressed the need for caution in associating postanaesthetic jaundice and hepatitis with any one factor.

Our patient developed unexplained pyrexia and jaundice on three occasions (1974, 1975 and 1977). Thiopentone was used for induction in each instance, but halothane was used only on the first occasion. Owing to the fact that halothane may have been present in the rubber of the anaesthetic circuit on the second occasion, special care was taken to use new equipment on the third occasion. The available evidence seems to suggest that thiopentone was the causative agent. This is supported by the fact that when thiopentone was omitted from the anaesthetic for laparotomy in 1977, where the identical anaesthetic circuit was used, no jaundice occurred after operation.

The patient has no history of contact with infectious hepatitis, blood transfusion or taking oral contraceptives. A later test has revealed no abnormality in liver function. The changes in the liver biopsy were minor and non-specific, but the appearance did suggest a drug-induced metabolic lesion.

It was felt that a cutaneous provocation test would be of little value and an i.v. test unjustifiable.

The combination of thiopentone and halothane is frequently employed in anaesthetic practice and we would urge caution in attributing unexplained postoperative jaundice to halothane in such patients.

ACKNOWLEDGEMENTS

We wish to express our thanks to Dr Timothy Smith, F.F.A.R.C.S., Royal Berkshire Hospital, Reading, for his helpful advice and interest, and Dr H. Søgaard, Pathologist, Aarhus University, for his description and evaluation of the liver biopsy.

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HEPATITE FAISANT SUITE A L'ADMINISTRATION DE THIOPENTONE

RESUME

Un malade a contracté une pyréxie et une jaunisse après anesthésies répétées. Ceci laisse penser que le thiopentone en a été la cause. Cet incident souligne la nécessité d'être très prudent lorsqu'on associe la jaunisse et l'hépatite à l'halothane chez les malades qui ont reçu du thiopentone et de l'halothane.

HEPATITIS NACH THIOPENTON-VERABREICHUNG

ZUSAMMENFASSUNG

Nach wiederholter Narkose entwickelten sich bei einem Patienten Pyrexie und Gelbsucht. Der Befund liess darauf schliessen, das die Ursache dafur Thiopenton war. Durch diesen Vorfall wird unterstrichen, dass, wenn Gelbsucht und Hepatitis bei Patienten, die Thiopenton und Halothan erhalten haben, mit Halothan in Verbindung gebracht wird, Vorsicht geboten ist.

HEPATITIS CAUSADA POR TIOPENTONA

SUMARIO

Después de anestesias reiteradas, un paciente padeció de pirexia e ictericia. La evidencia hace pensar que la tiopentona fué el agente causante. Este incidente pone énfasis en la necesidad de ejercer prudencia al asociar la ictericia y la hepatitis con el halotano en pacientes a los cuales se ha administrado tiopentona y halotano.

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Leicester LE1 5WW

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Br. J. Anaesth. (1979), **51**, 805

CORRESPONDENCE

DIURNAL VARIATION IN CARDIAC ARREST

Sir,—The report by Eltringham and Dobson (1979) on the apparently diurnal variation in cardiac arrest is most interesting. One of the main problems with their information is the nature of their distinction between "cardiac arrest" and "death". Some definitions of cardiac arrest use such phrases as "unexpected cessation of heart action", "previously fit" or, more recently "*apparently* fit person", "not expected to die" and so forth. Such definitions are quite obsolete, like the "ABCD" resuscitation sequence (Gilston & Resnekov, 1971), although all are still widely propagated. The practical difference between cardiac arrest and death depends on whether or not resuscitation is attempted, or if attempted, subsequently abandoned. In an Intensive Care Unit (where a large proportion of their patients were treated) "cardiac arrest" is another way of saying the heart has finally stopped beating in a desperately ill patient, hardly an "unexpected" event! In other words, are patients more likely to die at certain periods of the day, or is it simply that during those hours there is a high chance of someone saying "he isn't really dead, it's just that his heart has stopped"? Despite the play on words, this is an important point, since, today, "death" is synonymous with "brain death".

This is the root of the dilemma, "to resuscitate or not to resuscitate" a patient with a distressing or incurable lesion, for if his brain is not yet dead, although his heart has stopped, then truly he is still "alive", and not to initiate cardiac massage may, philosophically, be closer to a sin of commission than one of omission! Ethical euthanasia perhaps? Equally interesting, but far more difficult to pursue, would be a record of the times of death outside hospital. Are their long-term survivors spread equally throughout the day? If so, then this would indicate a temporal emphasis on resuscitation. On the other hand, if the number of long-term survivors is largest at the peak periods of resuscitation, then we would need to add further questions to their already considerable list.

A. GILSTON
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Sir,—Thank you for the opportunity to comment on Dr Gilston's letter. I was interested in the points he makes, but I must point out that it was not our intention to go into the philosophical or semantic aspects of cardiopulmonary resuscitation. In addition, we did not use the words "unexpected" or "death".

M. DOBSON
Gloucester

BRUXISM

Sir,—Grinding and gnashing of the teeth (bruxism) is a habit that can occur consciously or unconsciously and also during sleep. Although the aetiology of the disorder is unknown, it has been found to occur more frequently in nervous, hyperactive and mentally retarded children.

Bruxism in children older than 2 years of age, who are undergoing mechanical ventilation for prolonged periods of time with nasotracheal intubation or tracheotomy, should be observed carefully. On occasion a child may attract the nurse's attention by making a grinding noise with the teeth, but in addition, it has been our experience that bruxism is an early, audible sign of distress caused by hypoxaemia or incorrect ventilation of the lungs.

A child who practises bruxism should be observed carefully to avoid erosion of the teeth.

S. GARCÍA-TORNEL
Barcelona

CENTRAL VENOUS CATHETER DESIGN AND MAINTENANCE COMPLICATIONS

Sir,—We read with interest the report of Drs Parulkar, Grundy and Bennett (1978) concerning the fracture of a float catheter. This prompted us to review similar complications which had been observed at this hospital over a period of 1 year with one type of conventional central venous catheter (Vygon Surcath Long-line 174.17). The catheters had been inserted by a variety of medical personnel and used for either central venous manometry or parenteral nutrition.

Fracturing of the catheter shafts with leakage of infusion fluids and subsequent colonization with *Candida albicans* was noted on several occasions (fig. 1A). In two patients, *Candida* was cultured from blood. This fault occurs following repeated flexion of the catheter by movement of the patient, inadequate fixation to the skin, or simply the weight of the attached infusion lines. In one case, the nursing staff had attempted to stop the leak by wrapping adhesive tape around the catheter (fig. 1B). Separation of the catheter from its hub occurred on five occasions. This was associated in two instances with the development of clinical symptoms and signs suggestive of bacteraemia (fig. 2A). These complications occurred between 12 h and 10 days after insertion and all catheters were removed upon detection of these problems.

Such events, although infrequent, emphasize the importance of constant vigilance in the maintenance of central venous lines after insertion. The problem of sepsis and the integrity of central venous catheters is well known. The danger of air embolism via a fracture in the catheter hub or faults in the i.v. infusion line has been reported (Ordway, 1974; Armstrong, Peters and Cohen, 1977). Catheter embolism has occurred following repeated flexion of the shaft. Sprague and Sarwar (1978) recently reported a case of catheter embolism occurring from faulty bonding of the catheter shaft to the hub. They demonstrated, furthermore, separation of the hub and shaft in a number of "Angicaths"

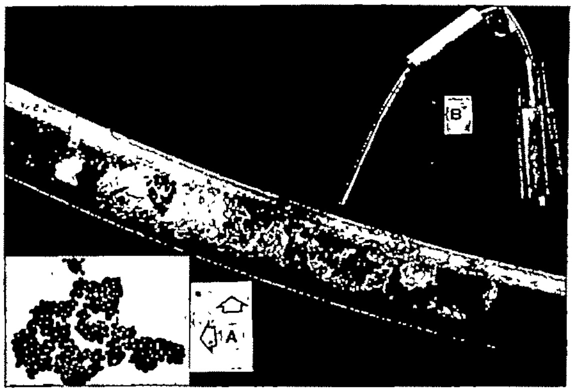

FIG. 1. A: *Candida* colonization of central venous catheter. B: Cracked and leaking catheter.

(Deseret) and "Quick-Caths" (Travenol) by incubating them for several days in a water bath at 37 °C and 42 °C.

Recently, skin tunnelling techniques for central venous catheters have been described when total parenteral nutrition is required. In one such procedure, the plastic hub is grasped and drawn subcutaneously using an artery forcep (Benotti et al., 1977). We feel that the junction between catheter hub and shaft should not be subjected to such excessive stress. In another subcutaneous tunnelling technique, the hub is cut off, the catheter tunnelled and the hub then reconnected (Powell-Tuck, 1978). Episodes of septicaemia have been observed following a similar technique when disconnection of the catheter shaft from the hub occurred (Keily, 1978). The preservation of a closed infusion system is essential to minimize the risk of air embolism or bacterial or fungal contamination. New catheters are being marketed for the provision of parenteral nutrition, in which the shaft is simply pushed on to a metal hub (fig. 2C). It is surely illogical that, having been improved by the advent of Luer-lock mechanisms (fig. 2B), the junction between the administration set and catheter has been replaced by a system in which the catheter can be disconnected from the hub at point "D" in the diagram (fig. 2C).

In our opinion, the design of central venous catheters must be improved to render them resilient enough to withstand normal clinical usage. There is clearly a need for a catheter constructed in unity with the hub which will allow smooth subcutaneous tunnelling to be accomplished when prolonged parenteral nutrition is envisaged.

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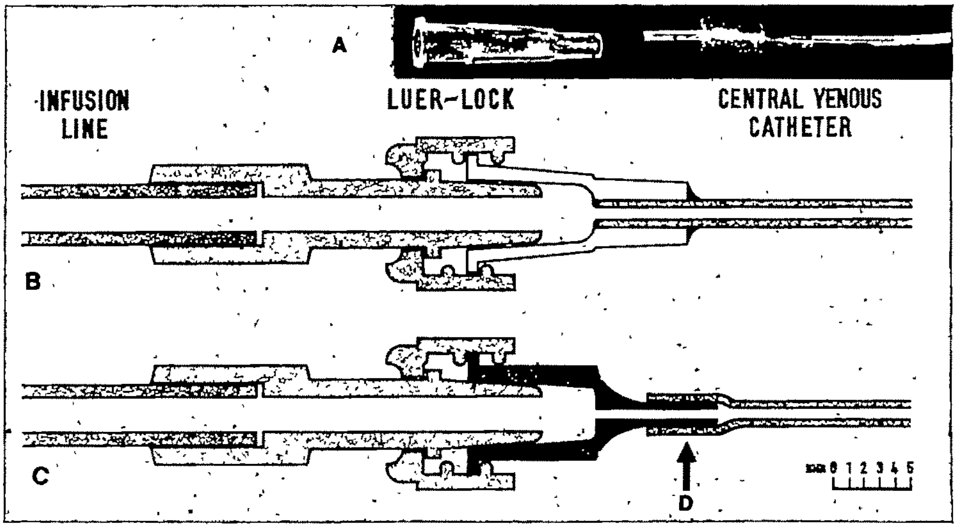

FIG. 2. A: Hub disconnection. B and C: Current catheter hub designs.

REGURGITATION AND ASPIRATION

Sir,—Dr Scott (1978) postulates that, where there is regurgitation of gastro–oesophageal contents into the pharynx, there exists in spontaneously breathing anaesthetized patients a mechanism for preventing irritant fluid reaching the smaller bronchi and that this mechanism is absent in paralysed patients. However, there is also a mechanism (present in spontaneously breathing anaesthetized patients and absent in paralysed patients) which prevents reflux into the pharynx of any material present in the oesophagus. This latter mechanism depends upon the muscle tone of the cricopharyngeal sphincter. This tone is present in the majority of patients even at relatively deep levels of anaesthesia when the patient is not paralysed.

Some years ago I studied the pattern of relaxation of the cricopharyngeal sphincter in response to suxamethonium (Davies, 1963). The loss of tone in the sphincter following the injection of a large bolus of suxamethonium was examined in 50 adult patients using a 1.5-cm diameter lax, water-filled balloon attached to a low inertia mercury manometer. The patients were anaesthetized with thiopentone 250 mg followed by nitrous oxide, oxygen and halothane. Of the 50 patients, 26 were known to have been at a level of anaesthesia at least as deep as plane II (Stage III). In these 26, decrease in balloon pressure following paralysis ranged from zero to 48 cm H_2O. The median value was 18 cm H_2O. In 21 of the 26 the decrease was greater than 10 cm H_2O.

A lax balloon 1.5 cm in diameter does not give an accurate measure of the tone present in the closed sphincter. However, these results suggest that, in the majority of instances, a patient undergoing inhalation anaesthesia will have a sphincter tone which is considerably greater than during full neuromuscular blockade and this would tend to prevent reflux of oesophageal contents into the pharynx.

Whether or not the trachea should be intubated in a patient with a full stomach depends on the type of operative procedure. Where a patient is to undergo a procedure requiring only a short, light anaesthetic, a non-intubation technique may be favoured. However, for major abdominal surgery, one must balance the dangers of intubating the trachea against those of maintaining prolonged anaesthesia without a safeguarded airway. If endotracheal intubation is to be undertaken, it may well be that this could be most safely performed using a purely inhalation technique and without the aid of muscle relaxants.

D. DENISON DAVIES
London

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CAROTID ARTERY PALPATION DURING INTERNAL JUGULAR VEIN CANNULATION AND SUBSEQUENT VENTRICULAR FIBRILLATION

Sir,—One of the hazards of cannulation of the internal jugular vein is puncture of the carotid artery. To avoid this, and to help in locating the vein, the artery may be sought beforehand (English et al., 1969; Mostert, Kenny and Murphy, 1970; McConnell and Fox, 1972). We describe a case where palpation of the artery near the carotid sinus was followed by ventricular fibrillation.

A 61-year-old-man was admitted to hospital for a coronary artery bypass graft for ischaemic heart disease. He had been taking propranolol 80 mg three times daily until the day of operation.

Premedication comprised papaveretum 15 mg, hyoscine 0.3 mg and droperidol 5 mg. The heart rate was 40 beat min^{-1}, in sinus rhythm (SR), and the arterial pressure was 190/100 mm Hg. Atropine 0.3 mg i.v. was given, and the heart rate increased to 50 beat min^{-1} SR. Induction of anaesthesia with papaveretum 20 mg and thiopentone 250 mg was uneventful; endotracheal intubation was performed after the administration of pancuronium 8 mg. Heart rate and arterial pressure remained unchanged.

The patient was tipped 20° head down and the surface markings of the right internal jugular vein were mapped out. The right carotid artery was not palpable at the root of the neck, but it was found opposite the thyroid cartilage at the level of proposed venepuncture. At the moment of palpation tachycardia developed (e.c.g. showed 200 beat min^{-1}) which changed rapidly to ventricular fibrillation. The heart was defibrillated successfully with 200 J. An antecubital fossa vein was used for insertion of a central venous line. The operation of coronary artery bypass grafting was successful. After operation, the patient denied symptoms of previous carotid sinus syndrome.

Carotid sinus massage may have a variable effect on the rhythm of the heart. Scherf and Schott (1973) described factors including: (1) the site of stimulation (on the carotid sinus or below it), (2) if stimulation causes vagal excitation or sympathetic inhibition and (3) the condition of the heart, particularly its rhythm at the time of stimulation. They described a case of ventricular tachycardia following carotid sinus massage for paroxysmal supraventricular tachycardia, and cases of ventricular fibrillation following carotid sinus massage in digitalized patients.

It is possible that in our patient palpation of the carotid artery stimulated the carotid sinus. The patient was already receiving propranolol, and had been given hyoscine with the premedication. These drugs could have caused bradycardia before induction of anaesthesia. Further vagal stimulation from the carotid sinus may have allowed ectopic ventricular foci to cause escape beats.

We have no e.c.g. tracing to support this explanation and the recent injection of atropine also casts doubt on our hypothesis, but until the carotid artery was palpated, the patient was in sinus rhythm and after palpation he developed ventricular tachycardia.

In future, we will identify the carotid artery with care.

J. S. SPRIGGE
G. D. G. OAKLEY
London

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SIMPLE RESUSCITATION OF THE NEONATE

Sir,—Resuscitation of the newborn during Caesarean section or normal labour is a prime duty of the anaesthetist. Not uncommonly, neonates do not commence rhythmic respiration and require artificial ventilation. It is generally recognized that mouth-to-mouth or mouth-to-nose resuscitation is the most satisfactory method available for emergency use but the technique is aesthetically unpleasant and difficult in small babies.

To overcome this problem, I have devised a simple resuscitator, the components of which are available in every operating theatre. These comprise (fig. 1) a mask (infant inflatable rubber face mask), a connector and a mouth piece, the last two being accessories from a Bird's Respirator.

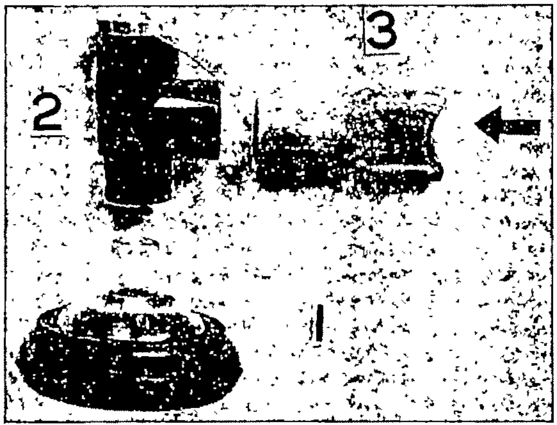

FIG. 1. Simple resuscitator for the neonate.
1 = mask; 2 = connection; 3 = mouth piece.

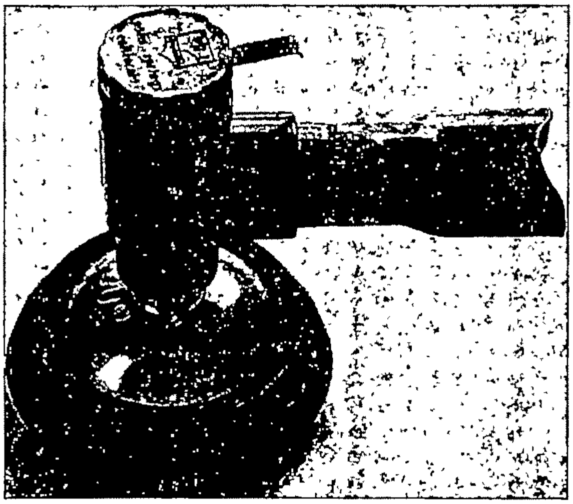

FIG. 2. The device assembled.

All these components can be assembled easily into one device (fig. 2) which is simple, light and comfortable. I have used this for resuscitation of neonates over the past 6 months, with encouraging results.

C. V. SINGH
Garyonius
Libya

TEST DOSES IN EXTRADURAL ANALGESIA

Sir,—I feel the letter from Dr J. A. Stirt (1978) regarding the use of a test dose in extradural block requires comment. If I have understood him correctly, he made his diagnosis that the extradural catheter had entered the subarachnoid space because fluid dripped back some minutes after the last injection, and on analysis this contained glucose at a concentration midway between that found in cerebrospinal fluid and blood. Neither of these points is valid.

It is a quite common experience to find fluid dripping back from the end of an extradural catheter if the end is left open to the atmosphere. Such dripping may continue for some time. Rapid changes occur in the injected fluid after entry into the extradural space. Local anaesthetic is absorbed quickly and there will be a tendency for all blood constituents which can cross capillary walls to equilibrate with the injected solution. Thus, it is no surprise that, after injecting a solution containing no glucose, there should be a measurable amount of glucose present 10 min after injection. Some years ago I collected fluid in this way from a number of patients undergoing extradural block. When analysed for lignocaine (2% had been injected) the concentration had always decreased, being as little as 0.5% 10–15 min after injection.

The events in the case of Dr Stirt can all be satisfactorily explained as a correct injection into the extradural space. A limited block was produced by a moderate dose of local anaesthetic and extended two segments higher by adding a further dose.

This case, far from strengthening the case for a test dose, in fact weakens it.

D. B. SCOTT
Edinburgh

REFERENCE

Stirt, J. A. (1978). Test doses in extradural analgesia. *Br. J. Anaesth.*, 50, 1267.

Sir,—Thank you for the opportunity to reply to Dr Scott's letter. He feels my assessment of a clinical situation as a transdural migration of an extradural catheter is incorrect.

The question arises of whether or not the timing and rate of fluid return from the external end of an extradural catheter is of diagnostic significance in regard to the location of its internal orifice. I believe it is. In the case I described pink fluid returned at the rate of 1 drop every 3 s beginning 10 min after the last injection of anaesthetic. This rate of return occurred despite the fact that the end of the catheter was tightly capped and not "left open to the atmosphere", and was far more rapid than that which occurs normally. In addition, return began 10 min after the last injection of local anaesthetic and not immediately. Since local anaesthetic is quickly absorbed, as Dr Scott points out, any fluid return would be expected to be maximal immediately following injection, not 10 min later.

In addition, it should be noted that a rapid decrease in extradural lignocaine concentration following injection into the extradural space does not imply a corresponding increase in extradural space glucose concentration. The two molecules are quite dissimilar chemically, their vascular permeabilities differ, and their transmural capillary transport has not been linked. The low values for lignocaine concentrations in the extradural space 10–15 min after injection probably result from transdural diffusion of lignocaine into the subarachnoid space and spinal cord.

I have attempted to resolve this question more definitely in females in early labour by measuring extradural space glucose concentration 10 min after injection of 12 ml of normal saline solution. Unfortunately, I was unable in five attempts to aspirate any fluid for analysis, no doubt as a result of rapid absorption and spread. This unexpected result further supports my contention that sudden rapid fluid return via an extradural catheter 10 min following anaesthetic injection should be interpreted as a sign of transdural catheter migration.

For all these reasons, I continue to feel that the correct diagnosis in my reported case was subarachnoid migration of an extradural catheter. The second injection of local anaesthetic without a test dose fortunately preceded entry of the catheter into the subarachnoid space, but by less than 10 min. A subsequent injection would most probably have resulted in a total spinal blockade.

These points reinforce my strong opinion that a test dose should precede all attempted injections into the extradural space.

JOSEPH A. STIRT
Los Angeles

ANAESTHETICS AND PORPHYRIA

Sir,—Drs Parikh and Moore (1978) recently reported that, in an *in vivo* rat model, the activity of δ-aminolaevulinic acid synthetase is increased by enflurane and unaffected by diazepam. The authors concluded that agents, such as enflurane, which induce activity of this enzyme should not be administered to patients with acute prophyria. We feel this conclusion is uncertain, particularly in relation to humans with actue intermittent porphyria, as demonstrated by this case report.

A 62-yr-old man with alcoholic cirrhosis had an episode of acute intermittent porphyria associated with the administration of diazepam. The porphyria was characterized by an ascending paralysis which necessitated ventilatory support for 21 days. Laboratory test results revealed an increased urine porphobilinogen concentration, a positive Watson–Schwartz test and a urinary δ-aminolaevulinic acid concentration of 62 mg per 24 h (normal concentration is less than 4 mg per 24 h). After treatment, he recovered satisfactorily. However, 15 months later, the patient was readmitted to the hospital because of recurrent upper gastrointestinal bleeding caused by oesophageal varices. Subsequently, he had an 11-h operation for spleno–renal shunt with enflurane–nitrous oxide (50%) anaesthesia. The inspired enflurane concentration was maintained between 1 and 3%. After the anaesthesia and surgery, he recovered satisfactorily with no symptoms or laboratory evidence of acute intermittent porphyria.

D. R. STONE
E. S. MUNSON
Gainesville, Florida

REFERENCE

Parikh, R. D., and Moore, M. R. (1978). Effect of certain anaesthetic agents on the activity of rat hepatic δ-aminolaevulinate synthase. *Br. J. Anaesth.*, **50**, 1099.

Sir,—We are grateful to you for allowing us to reply to the comments of Drs Stone and Munson on our study. The short story of their case emphasizes the problems in establishing safe use of drugs in porphyria. A hereditary predisposition to the disease may be precipitated by many factors, for example drugs, alcohol, diet and endocrine status. However, administration of even an established induction agent such as thiopentone does not invariably lead to an attack (Ward, 1965). The uneventful use of enflurane and an acute attack of porphyria associated with the use of diazepam in a patient suffering from alcoholic cirrhosis do not indicate the safety or danger of administering these drugs in all patients suffering from porphyria.

An objective measurement to "screen" drugs for use in porphyrias is necessary. The changes in the activity of δ-aminolaevulinate synthase in rat liver *in vivo* (as in our study), or in chick embryo liver cell cultures *in vitro*, have been used for this purpose. It is difficult to extrapolate results from such animal studies to patients, but rat liver system is generally thought to be much less sensitive and less likely to give false positive results than chick embryo liver cell cultures (Tschudy, 1975). Studies of the effects of anaesthetic agents on the activity of δ-aminolaevulinate synthase and on other aspects of haem biosynthesis assist in the rational management of anaesthesia in porphyria. In the present circumstances we consider it advisable to avoid the use of anaesthetic agents known to induce the activity of δ-aminolaevulinate synthase when alternative agents are readily available.

R. K. PARIKH
M. R. MOORE
Glasgow

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Ward, R. J. (1965). Porphyria and its relation to anesthesia. *Anesthesiology*, **26**, 212.

PULMONARY MECHANICS DURING GENERAL ANAESTHESIA

Sir,—There are errors in the paper by Dr Dohi and myself (1979). Because of circumstances beyond the control of the editor, the publisher or the authors there were many corrections which did not reach the editor's desk until after publication of this paper. The authors do not believe that either the substance or the conclusions of the paper are affected. However, there may be some investigators who are confused concerning details of omissions and changes. If they will contact the authors, the corrected version of this paper will be mailed to them.

M. I. GOLD
Miami

REFERENCE

Dohi, S., and Gold, M. I. (1979). Pulmonary mechanics during general anaesthesia. The influence of mechanical irritation on the airway. *Br. J. Anaesth.*, **51**, 205.

FITNESS TO DRIVE AFTER ANAESTHESIA

Sir,—In the third edition of *Medical Aspects of Fitness to Drive* (published by the Medical Commission on Accident Prevention), Dr J. A. Havard, Deputy Secretary, B.M.A. writes, "With most general anaesthetics, it is safer to advise against driving for 48 hours afterwards."

The apparent divergence of this advice from usual practice in Britain, coupled with the eminence of the author, has occasioned several queries from anaesthetists and the matter has come before the Anaesthetists' Sub-Committee of the C.C.H.M.S. and the Council of the Association of Anaesthetists.

The time taken to achieve safe "road-worthiness" varies widely between different anaesthetic agents and depends on dose, metabolic fate of the agent and individual variation. It would be rare for an interval of 48 h to be necessary. There is no interval that could be recommended unconditionally for all situations; nevertheless, an interval of 24 h or "after a night's sleep" would be regarded normally as sufficient. Dr Havard's opinion must be presumed to be a personal one.

P. J. F. Baskett
Honorary Secretary,
Association of Anaesthetists
M. D. Vickers
Chairman,
Anaesthetists' Sub-Committee
of the C.C.H.M.S.

EXTRADURAL ANALGESIA OR GENERAL ANAESTHESIA FOR ELECTIVE SECTION

Sir,—Prompted by the interesting article by Professor Downing and his colleagues (1979), may I offer some comments upon this subject? As these workers record and, as we suggested previously in the paper to which they refer (James et al., 1977), the optimal direction of tilt can rarely be pre-determined (possibly asking the patient which side she has preferred to lie on during the final trimester will provide a clue—we are at present investigating this possibility). The anaesthetist must observe the response of the mother to the first top-up of local anaesthetic in order to determine which direction of tilt is associated with the least aorto-caval compression. The rather considerable degree of neonatal metabolic acidosis found by Downing and colleagues (1979) in their extradural series was predominantly an infusion acidosis, of uncertain origin (possibly reflective of maternal discomfort or hypotension), but aorto-caval compression will have contributed to this.

The frequencies of maternal discomfort and hypotension among the patients who received extradural block were disappointingly high, and were close to those which have been quoted to me in personal conversation with anaesthetists elsewhere in this country and in North America. I believe that they reflect a failure to refine the technique of administration. It has been our custom during the past 2–3 yr to inject bupivacaine 0.5% plain into the extradural space in incremental doses. I suggest that it is partly as a result of this that only one patient among our most recent 100 who have received extradural block for elective section has developed hypotension to an extent which required the administration of ephedrine. I suggest that a phased extension of vasomotor blockade allows time for restabilization of maternal cardiovascular dynamics without an undesirable decrease in arterial pressure.

Another aspect of this technique is also useful in this regard. Following upon advice given to me by Dr Donald Moir of Glasgow, we now administer the first of the incremental doses (customarily 10–15 ml) with the patient in the semi-sitting (reclining) position. This again reduces the likelihood of hypotension, but it has served almost to eliminate unsatisfactory analgesia. Previously we had noted, in common with many other anaesthetists, that patients would frequently complain of suprapubic pain or discomfort when the uterus was marsupialized preparatory to suture. After putting Dr Moir's advice into practice, this phenomenon has become a rarity, and only six of our most recent 100 patients have required supplementary analgesia during the operation. It is noteworthy that, of these six patients, four received a total of only 16–20 ml of bupivacaine. Our dose of bupivacaine, given incrementally, is considerably greater than that generally reported by others. It ranges from 15 to 55 ml (mean 25.6 ml), 50 of our recent 100 patients having received 20–25 ml and 32 receiving 26–30 ml. The sensory block rarely extended more cephaled than T4, no maternal complications ensued, and in the absence of obstetric pathology all the infants had an Apgar-minus-colour score of 8/8.

In summary, I believe that if the local anaesthetic is administered in incremental doses, with careful assessment of the optimal posture for avoiding or reducing aorto-caval compression and of the attainment of an effective spread of sensory block, the occasional disappointments encountered in association with this method of anaesthesia for section will be markedly reduced in number. Such modifications undoubtedly are time-consuming. However, whilst I appreciate that this could cause inconvenience in the context of general or gynaecological surgery, I would not accept that to spend 30–45 min over the anaesthetic preparation of a patient for elective section poses an intolerable burden upon the smooth running of an Obstetric Unit.

J. Selwyn Crawford
Birmingham

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Downing, J. W., Houlton, P. C., and Barclay, A. (1979). Extradural analgesia for Caesarean section: comparison with general anaesthesia. *Br. J. Anaesth.*, **5**, 367.

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Br. J. Anaesth. (1979), **51**, 811

BOOK REVIEWS

Artificial Ventilation for Pulmonary Disease. By M. A. Branthwaite. Published by Brompton Hospital, London. Pp. 40; illustrated, indexed. Price £1.

The author writes in her foreword, "the desire to produce a short, practical handbook has resulted in a text which is didactic, at times over-simplified and which rests heavily on current practice at the Brompton Hospital". It is a fair comment on a better than fair booklet. This reviewer's views and prejudices were offended a little from time to time, but the reason was usually that he was thinking of respiratory failure in the broader sense whereas Dr Branthwaite was correct in writing strictly to her title, "Artificial ventilation *for pulmonary disease*".

Chapter 1 describes briefly and simply the concept of the pressure generator and flow generator and discusses how their performance is affected by technical aberrations or pulmonary abnormality. The Brompton ventilator is also described at some length. Chapter 2 concerns "Matching man and machine". Here is excellent clinical advice and commentary such as, in the section on chronic airways obstruction with respiratory failure, the maxim "introduce no sudden change" followed by a list of six very pertinent reasons.

Chapter 3, on "maintenance of the airway", will contain few new messages for practising anaesthetists, but chapters 4 and 5 are a fine distillate of basic principles of respiratory intensive care. Could it be, however, that a rather ignorant non-anaesthetist might understand (pp. 25, 26 and 31) that pancuronium is just another sedative and that some disaster might arise therefrom? For instance, in the section on asthma: "It is preferable to allow long-acting sedatives to wear off before extubation, achieving quiescence during the last six hours or so with 50% nitrous oxide. This alone is often insufficient and a small dose of diazepam ± pancuronium may be needed too".

The overall impression is that there is a lot of really good stuff in this booklet. It is recommended as very worthwhile and remarkably pleasant reading.

E. A. Cooper

Epidural Analgesia. By P. R. Bromage. Published (1978) by W. B. Saunders Co., Philadelphia. Pp. 725; illustrated. Price £21.75.

Dr Bromage notes in his introduction that 24 years have passed since the publication of what he describes as the "preliminary version" of this book. What a transformation! Books inevitably grow in price, and almost inevitably in size; but here is one which has also grown in stature to such an extent as to be unrecognizable. Dr Bromage also tells us in his Acknowledgements that he wrote the present book during a period of sabbatical leave. The purpose of sabbatical leave, as usually understood, is to enable members of academic staff to draw breath and obtain much needed refreshment. Dr Bromage may have felt refreshed or exhausted after his labours; he should at any rate have felt proud, for as judged by results there can rarely have been a period of sabbatical leave that was better spent. It is unusual nowadays for a book of this size and complexity to be written by a single author; this is a truly individual effort and in terms of the coherence of style and presentation the advantages are clear.

I have not yet found time to read the 725 pages of this book in detail and in any case it would be inappropriate to write a critical review in the finicky sense. I am more inclined to pay tribute to what seems to me a very substantial personal achievement on the part of the author, in producing what must rank as the standard work of reference on extradural analgesia for some considerable time to come.

The detailed coverage of the book includes history, anatomy, pharmacology, mechanism of action and some chapters concerned with technique. This is followed, interestingly, by a section on physiology, then clinical applications and complications. There is a final chapter on teaching techniques, which includes brief critiques of some of the available material in video tape, film and tape–slide form. There are excellent tables, graphs, diagrams, x-rays and other illustrations throughout, drawn from the literature and originally produced. Each chapter contains a wealth of data and a very substantial collection of references. The text includes much good critical discussion of this published work and if the reader is stimulated or provoked by some of the statements that are made, he often at least has a source indicated for him.

Apart from its value for reference and theoretical discussion, Dr Bromage's book offers a great wealth of practical advice which comes very clearly from one who has had an enormous experience with extradural techniques. This shows itself not only through the author's enthusiasm for the method, which is evident enough, but also in his constructively realistic account of its limitations and potential hazards in the management of chronic pain.

As would be expected from Dr Bromage, this book has a literary style of its own which is leisurely, often charming and perhaps sometimes a little irritating, although this will be a matter of personal taste. How nice, though, instead of some Americanized verbiage about the variability of sacral anatomy, to read: "a stroll among the skeletons of any anatomy department will reveal the rich variety of contours surrounding the sacral hiatus". It is almost a shame that the subject matter does not allow the author to do all the time what he can sometimes do at his best.

Each chapter is headed by a quotation, and these come from a wide range of sources. My favourite must be the one from Lin Yutang which, appropriately, introduces the chapter on teaching techniques, and which might serve as a compliment to the author himself: "The aim of education or culture is merely the development of good taste in knowledge and good form in conduct. The cultured man or the ideal educated man is not necessarily one who is well-read or learned, but one who likes and dislikes the right things."

J. Parkhouse

Drugs in Anaesthetic Practice, 5th edn. By M. D. Vickers, F. G. Wood-Smith and H. C. Stewart. Published (1978) by Butterworths, London. Pp. 604. Price £16.95.

Many anaesthetists, both in the United Kingdom and abroad, will welcome the fifth edition of this well-known textbook. Previous editions have earned generally eulogistic reviews and this edition seems to be even better than its predecessors. It can be confidently recommended to anaesthetists both senior and junior, since it fulfils a real need.

Although this is a book on drugs in anaesthetic practice the section on general anaesthetic agents comprises only about one-tenth of the text—in fact the section on antimicrobials is nearly as long. Chloroform earns only a page and a half (the section on digoxin is twice as long) and ethyl chloride only half a page (the section on sodium cromoglycate, again, is twice as long). This illustrates the authors' obvious determination that this long-lasting book (17 years) will not be allowed to ossify, but will be kept up to date. *Drugs in Anaesthetic Practice* also illustrates the scope of modern anaesthesia. Nowadays the anaesthetist uses, or is concerned with, a wide range of the most dramatic and powerful of the therapeutic agents. In the book will be found, therefore, sections on cardiovascular drugs, thrombolytic agents, diuretics, uterine stimulants and many others.

Progressively since the first edition, old material has been pruned with a fair degree of ruthlessness and new material added. The preface tells us that, in this edition, 29 monographs on drugs present in the fourth edition have been removed and 11 new monographs introduced. The authors are thus determined not to solve the problem of new material merely by making the book larger; they are prepared to accept the much more difficult discipline of bringing in new things to a considerable extent at the expense of leaving old things out. This doubtless is, in the long run, the only way to manage a book of this sort, but it is surprising how frequently authors of textbooks show an undue reverence for the old-fashioned and the out-of-date.

The book also contains, of course, accounts of newer drugs such as enflurane, etomidate and lorazepam. One of the great values of an up-to-date textbook is that it enables those who have fallen by the wayside and have not kept abreast of the literature in their subject to bring themselves quickly and painlessly up to date without having to delve into journals. If there be anybody in this situation (and most anaesthetists of consultant rank would agree that they are, to some extent) this edition should provide a pleasant and economical remedy. There is, in addition, a judiciously selected list of references, many of which are recent by the standards of textbooks, all of which tend to be a long time in gestation.

There is a subtle but discernible difference between a reference book and a textbook, although, obviously, there is often a tendency for the two to blend as the difference is far from clear-cut. As a work of reference *Drugs in Anaesthetic Practice* is much less comprehensive than, for example, Goodman and Gilman's mighty *Pharmacological Basis of Therapeutics*. Nevertheless *Drugs in Anaesthetic Practice* could well be useful as a reference book and many circumstances can be envisaged in which it would be useful as a textbook.

Perhaps the main group interested in this book will be those taking the primary F.F.A. (it is interesting that virtually no pharmacology is demanded by the primary F.R.C.S.). For this group the book is virtually tailor-made. Certainly there is none better.

J. E. Utting

The Liver and Anaesthesia; vol. 3 in the series *Major Problems in Anaesthesia*. By L. Strunin. Published by W. B. Saunders Company Ltd. Illustrated. Price £10.00.

This monograph is essential reading not only for those anaesthetists who are seeking a higher qualification, but also for those responsible for the training of junior staff. In addition those clinicians who care for patients with jaundice would also benefit from reading this book.

Although occasionally a sentence is virtually incomprehensible, for the most part the text is easy to read, partly because it is well set out and partly because diagrams which are highly instructive complement the script. Indeed, a few more diagrams at the expense of some of the seemingly interminable tables would substantially improve the presentation.

The material is presented in two parts; the first, which occupies just over one-third of the total text, is concerned with basic principles. The anatomy and physiology of the liver are described in detail and this description is followed by chapters on liver function tests, liver blood flow and drug metabolism. The section of drug metabolism which includes drug reactions is reasonably comprehensive and is well annotated.

The remainder of the book deals with practical considerations and discusses such problems as viral hepatitis, the jaundiced patient and hepatic dysfunction after operation. The section on postoperative hepatitis is a well balanced presentation and the reader does not have to accept the whole interpretation to appreciate the logic of the argument. The description of the effect of chloroform on the liver, although informative, is less well balanced and many relevant references, particularly to experimental studies carried out during the inter-war years, have been omitted. In this respect a more general criticism is that a more discriminating approach to references would have been helpful. The reader needs to know what value should be placed on the material quoted and in a number of instances papers that were of doubtful significance are given the same status as more definitive work.

One of the difficulties that faces any author who is attempting to produce an authoritative text is how to approach his task. Some writers present a highly subjective and possibly prejudiced text, others try to be objective and exclude their own particular bias and even their own viewpoint. The latter are more factual, but the former are more enjoyable to read. Professor Strunin has adopted the former approach which is a pity because, however praiseworthy his attitude, his text loses emphasis. Furthermore, with his background and experience in the field he is entitled to be more forthright, even if his views are controversial.

J. P. Payne

Mechanical Misadventures in Anaesthesia. Edited by G. M. Wyant. Published by University of Toronto Press. Pp. 174; illustrated. Price $15.

Professor Wyant has set out with the clearly stated purpose of drawing attention to anaesthetic mishaps that are known to have been caused by ill-designed or misued apparatus. Within the compass of some 170 pages, clearly printed, well illustrated, and including an extensive bibliography, he has fully achieved his aim. The background having been set by Dr O. P. Dinnick in a foreword which stresses the multifactorial aetiology of most anaesthetic mishaps, the full spectrum of anaesthetic apparatus hazards is set out in a logical progression and with devastating clarity. The sequence of presentation takes the reader through the gas flow path from medical gas pipelines to equipment in contact with the patient. A comprehensive chapter by Dr D. A. Pelton on "Non-flammable gas pipeline systems" and a section by Dr J. K. Scott on "Scavenging devices" are included.

The author is primarily concerned with situations of supply and equipment failure rather than with the precise mechanisms designed to forestall such failures or remedy their consequences. Nevertheless, mention is made of fail-safe systems and warning devices, if only to point out their own fallibility.

Professor Wyant has, for many years, been concerned not only with the study of anaesthetic mishaps, but also with the attempts which have been made to establish international standards for anaesthetic equipment as a contribution to the elimination of hazards. Unfortunately, very few anaesthetists are conversant with the efforts which have been made in this field and it is all the more welcome therefore to find that this book contains an up-to-date statement of the "standards" position in many countries.

So long as apparatus is used hazards will arise, and there will always be new ones. Safety must, to a large extent, depend on the anaesthetist being aware of the fact that things can go wrong and this book will do much to increase this awareness. It should be studied as a dreadful warning by everyone who has anything to do with anaesthetic apparatus and investigation of the "untoward incident" in clinical practice.

Peter W. Thompson

Anaesthetics, Resuscitation and Intensive Care (5th edn). By D. Campbell and A. A. Spence (foreword by J. W. Dundee). Published by Churchill-Livingstone, Edinburgh. Pp. 261; indexed; illustrated. Price £5.00.

There can be little doubt that this book has been a popular filler of a common need. It first appeared in 1965 and was revised subsequently in 1968, 1971 and 1974. Clearly, a new version is due and Dr Alastair Spence has stepped into the gap left by the sad and early death of Walter Norris. The decision has been made to remain true to the original purpose and format and much of the material is therefore easily recognizable from the last edition. Thus the book lives up to its title. It covers anaesthetics at a basic level in 150 pages and devotes a further 80 to the other main activities of the professional anaesthetist in resuscitation and intensive care. It offers a text at the appropriate level and well proportioned for the undergraduate medical student in his brief attachment to the speciality of anaesthesia. The content and layout are also appropriate, as claimed, for specialist nursing staff in these fields. However, the reviewer has greater doubts as to the place of the book in the reading of residents, especially those with a serious career interest in anaesthesia or intensive thearpy.

The quality of production and presentation is pleasing and there are few typographical errors, but there are numerous minor blemishes and inconsistencies on which the student may stub his intellectual toe. "The anaesthetic machine is composed of four simple systems (figure 3.1)", yet the caption to figure 3.1 reads "diagrammatic representation of the five components of a simple anaesthetic apparatus". Is "pulmonary and arterial circulation" a true synonym for "pulmonary and systemic circulation"? Is "the patient's alveolar minute volume (usually 5–6 litres/min)" truly a reference to alveolar, or to respiratory minute volumes? Why should the doses of tubocurarine and gallamine be given in mg whilst those of alcuronium, pancuronium and fazadinium are given in mg/kg?

In short, this book reads as an up-dated text of the 60's and will keep its adherents. If part of its function is to stir medical students into seeing anaesthesia as a subject which is interesting, logical and progressive, there is a good case for a more radical revision of the next edition.

E. A. Cooper

Interpreting the Electrocardiogram. By James S. Fleming. Published by Update Books Limited, London. Pp. 135; illustrated; indexed. Price £6.75.

In the introductory chapter, the author stresses the integral relationship of the electrocardiogram with a patient's clinical condition and emphasizes that, ideally, it should be interpreted by the doctor who is responsible for the clinical care of the patient. This book, based on an early series in the journal "*Teach In*", has been planned as an introduction to the subject for those seeking guidance on the clinical assessment of the electrocardiogram. The majority of books devoted to this subject are designed as "pocket" volumes; the dimensions of the pages of this volume (28 cm × 20 cm) at once indicate that compactness has been considered to be of minor importance. Dr Fleming's clear and simple style of writing is complemented by the impression of spaciousness created by the general layout; it is a pleasure to read.

Each section of the book is short, well illustrated with clear diagrams and ends with a brief summary; electrophysiological concepts are deliberately omitted and the clinical orientation is emphasized as each section is followed by a series of electrocardiograms with brief clinical notes, demonstrating the features which have been discussed. Each topic leads logically to the next, and simple descriptions of the constituents of the e.c.g. are followed by sections on myocardial infarction, ischaemic heart disease and cardiac arrhythmia. Electrocardiographic changes seen in association with disordered electrolyte balance, endocrine disease and drug therapy are described, but the influence of anaesthesia and the effects of anaesthetic agents receive no attention. Despite this, the trainee anaesthetist seeking expertise and confidence in the clinical interpretation of the e.c.g., and the examination candidate, will benefit from a study of this book.

K. M. S. Dewar

Analgesic Drugs. By J. Parkhouse, B. J. Pleuvry and J. M. H. Rees. Published (1979) by Blackwell Scientific Publications, Oxford. Pp. 159; indexed. Price £5.

A concise and informative monograph on the currently employed analgesic drugs has long been overdue. As a result of intensive research a great number of new compounds have been released and more are no doubt on the way. This little book by Professor Parkhouse and his colleagues does more than classify the narcotic and antipyretic analgesics and elucidate their mechanisms of action and general pharmacology but, for good measure, includes an introductory chapter on the mechanisms of pain which is a model of brevity and clarity. The final section provides guidance on the statistical design and pitfalls of controlled clinical trials and should be compulsory reading for all those wishing to embark on these often troubled waters. The reviewer has only one minor criticism and that is that even this excellent monograph cannot hope to keep pace with all the recent advances, particularly new work on the endorphins and enkephalins. Two appendices, one on statistical samples and the other a tabular classification of the available drugs with their trade names and dosage, complete this text which is highly recommended.

Donald Campbell

Sleep Apnea Syndromes. By C. Guilleminault and W. C. Dement. Published by Alan R. Liss Inc., New York. Pp. 390; illustrated; indexed. Price $34.00

Disorders of respiration during sleep are the subject of much current interest. This volume brings together 24 contributions, most of which were presented at a Conference in July 1977, providing a summary of present knowledge, techniques and hypotheses as an impetus to further research.

The assembled papers cover aspects of sleep apnoea ranging from the symptomatology and physiology to the possible sites of obstruction and management. The papers by Lugaresi and colleagues on the clinical implications of snoring and by Henderson-Smart and Read on the vulnerability of the newborn to asphyxia illustrate the wider implications of an apparently esoteric subject. The detailed fibreoptic and polygraphic studies of the Stanford group elegantly display the site of airway obstruction during obstructive apnoea. The book closes with a general discussion and an appendix covering practical aspects of sleep monitoring.

The editors have largely avoided the almost inevitable duplication of material and have neatly summarized the discussion which follows each paper.

While unlikely to find a place on the shelves of department libraries, for those with an interest in the field this book represents an adequate summary of current knowledge and belief. The reference lists and practical advice render it a useful handbook and the many unanswered questions present a fertile course of future study.

C. D. Hanning

Pain. Its Nature, Analysis and Treatment. By M. R. Bond. Published (1979) by Churchill Livingstone Medical Text. Pp. 186. Price £3.95.

Pain is commonly regarded purely as a symptom of organic disease or injury. Professor Bond, in clear and concise terms, discusses the multifacetal nature of this complex, subjective experience and is at his best in dealing with the psychological, ethnic, social and environmental factors which influence pain behaviour. He emphasizes the importance of learning and personality traits and uses these as stepping stones to a chapter on the meaning of pain. There are introductory chapters on basic mechanisms and measurement followed, in Part II, by a clinical analysis of this common symptom. Once again the highlights are interrelationships between pain, emotion, mental illness and physical behaviour. The last part deals with physical and psychological methods of pain relief.

This eminently readable, modestly priced little book is written primarily for medical students in their final years and remedies a notable omission in the undergraduate curriculum. However, it should also be of considerable value and interest to a much wider circle of general practitioners, hospital doctors and nurses who are concerned in the management of pain patients. Certainly it should be compulsory reading for all anaesthetists and other workers in pain relief clinics and continuing care units.

M. Mehta

Pediatric Trauma. Edited by R. J. Touloukian. Published (1978) by John Wiley and Sons Inc. Pp. 637; illustrated; indexed. Price £24.95.

Twenty-two contributors chosen by Professor Touloukian have combined with the aim of describing "...in comprehensive detail all important trauma problems encountered in infants and children". This immense task is dealt with by devoting the first 177 pages to general considerations, and the remainder is directed to a consideration of specific injuries.

The early chapters contain information which is generally known to most workers and it is written in a rather superficial fashion. Some rather unnecessary line diagrams in Chapter 2 do nothing to dispel an impression of padding, and values quoted in ml/lb are irritating to a British reader. Most of the advice given with regard to evaluation and initial management are generalizations. The third chapter, on Psychologic Aspects, is well written and thought-provoking and the chapter on Radiologic Considerations presents a review of the x-ray changes which occur in trauma, of particular value to those who are not specialists in x-ray interpretation.

Perhaps the chapter of most interest to anaesthetists is that devoted to anaesthesia and intensive care. Unfortunately, only 28 pages are allowed for the consideration of this aspect of the subject and the presentation is necessarily rather generalized. Some errors occur and are irritating to a reader, for example on p. 144 Dr Sellick's name is spelt with only one l and in the same paragraph atropine is said to be indicated in order to decrease gastric reflux. Clichés which can be annoying abound in the text and often are not meaningful—on p. 117 "anaesthetic techniques should be chosen which permit appropriate emergence". These criticisms apart, the chapter gives the reader a useful insight into anaesthetic attitudes and practice in this area.

The sections of the book which are devoted to specific injuries are of very considerable interest and help to the non-surgical reader. As a background source of information for the anaesthetist they are invaluable. The section on cardiothoracic injuries is a good example and the information is well presented. The section devoted to injuries of the larynx and trachea, the subsequent complications and their treatment, can be singled out as an illustration of the useful information which many of these chapters contain.

This book is, therefore, one which can be of value to the anaesthetist, particularly as a reference book, and in it he will find many aspects of the treatment of the injured child which are of value to him.

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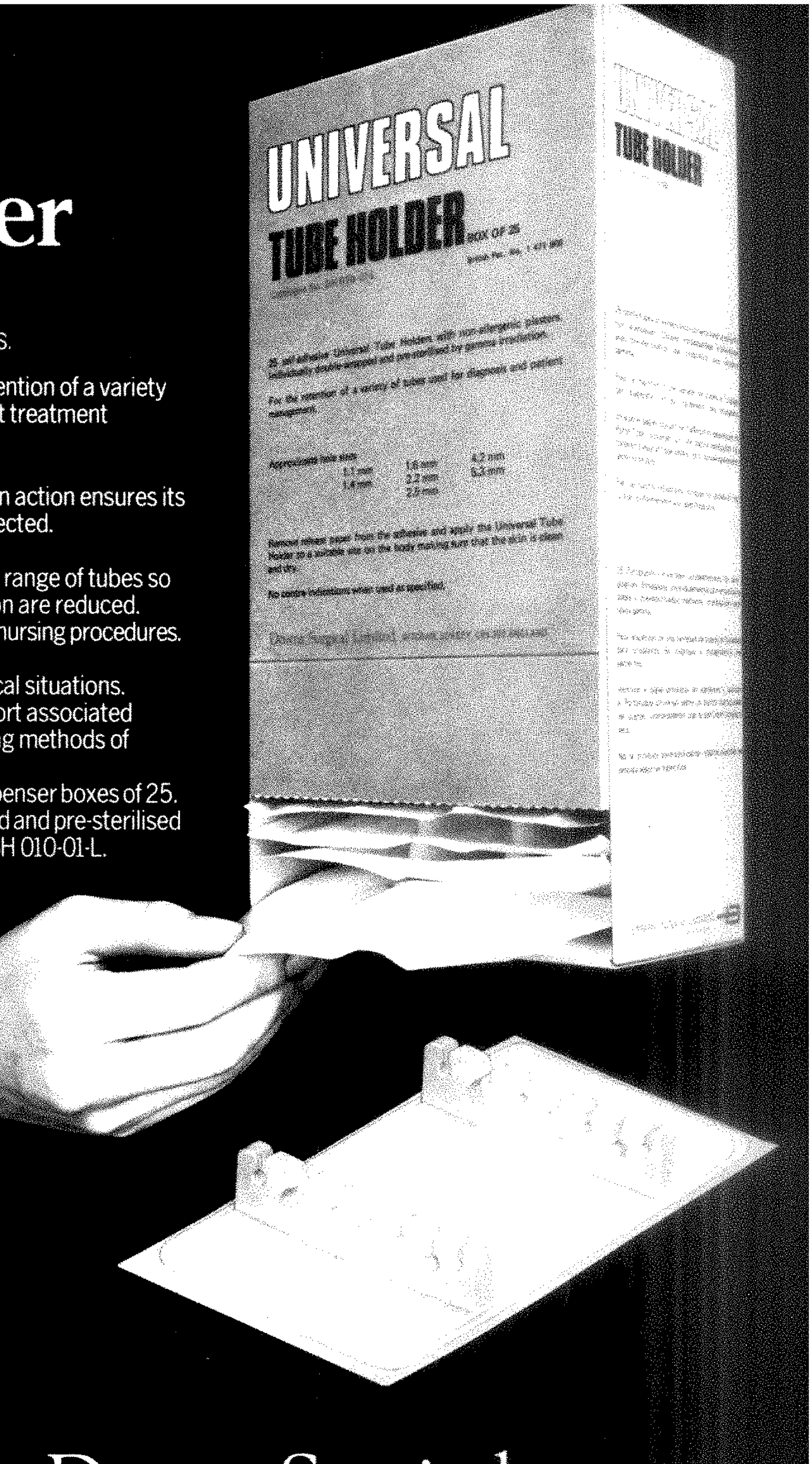

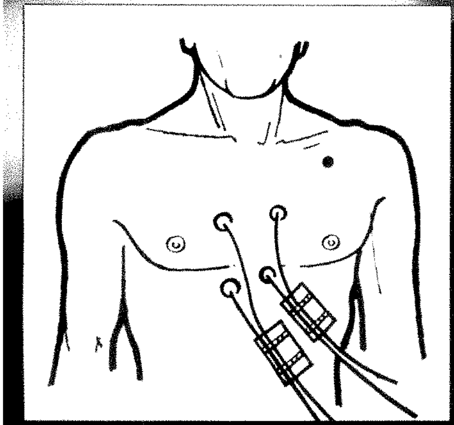

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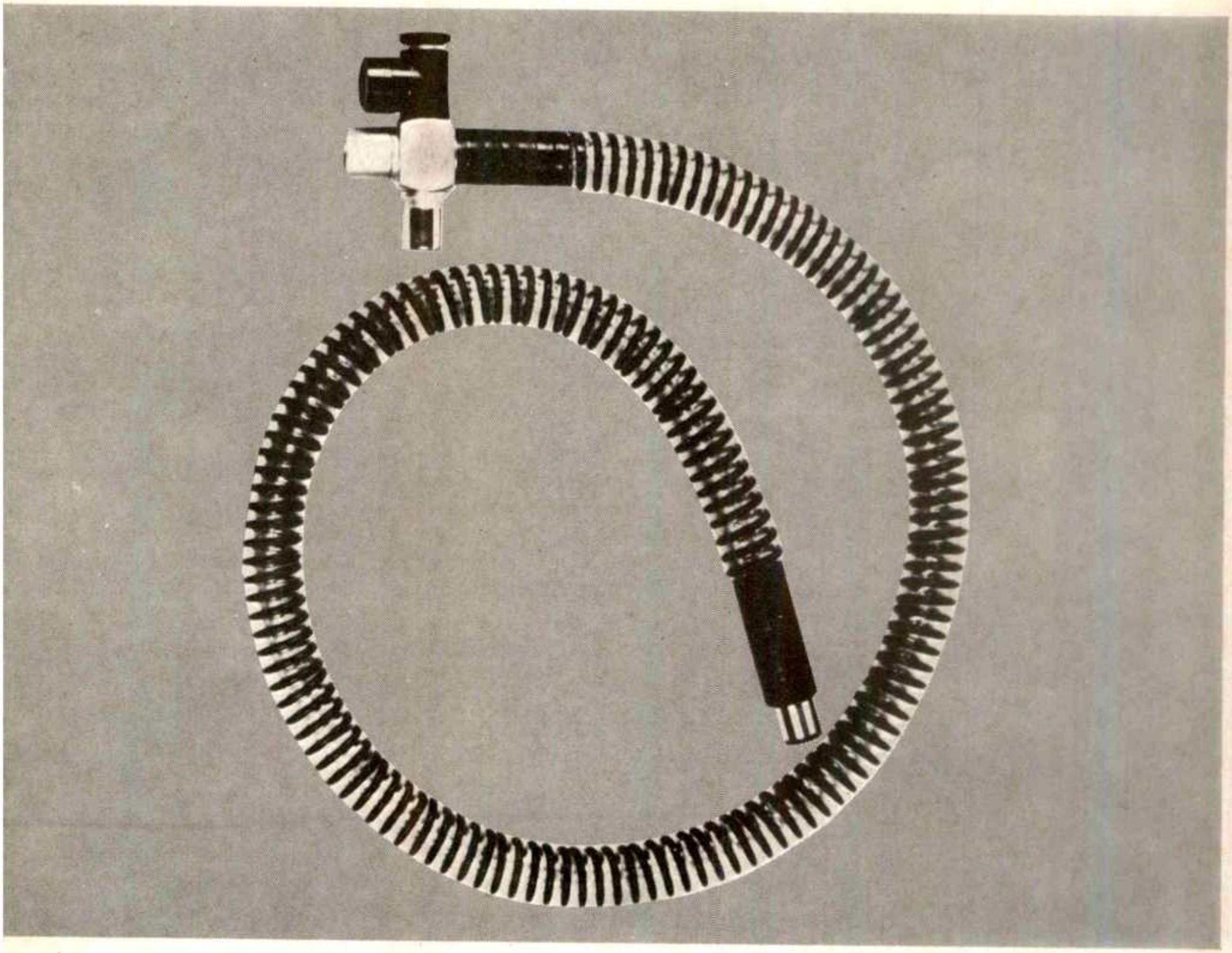

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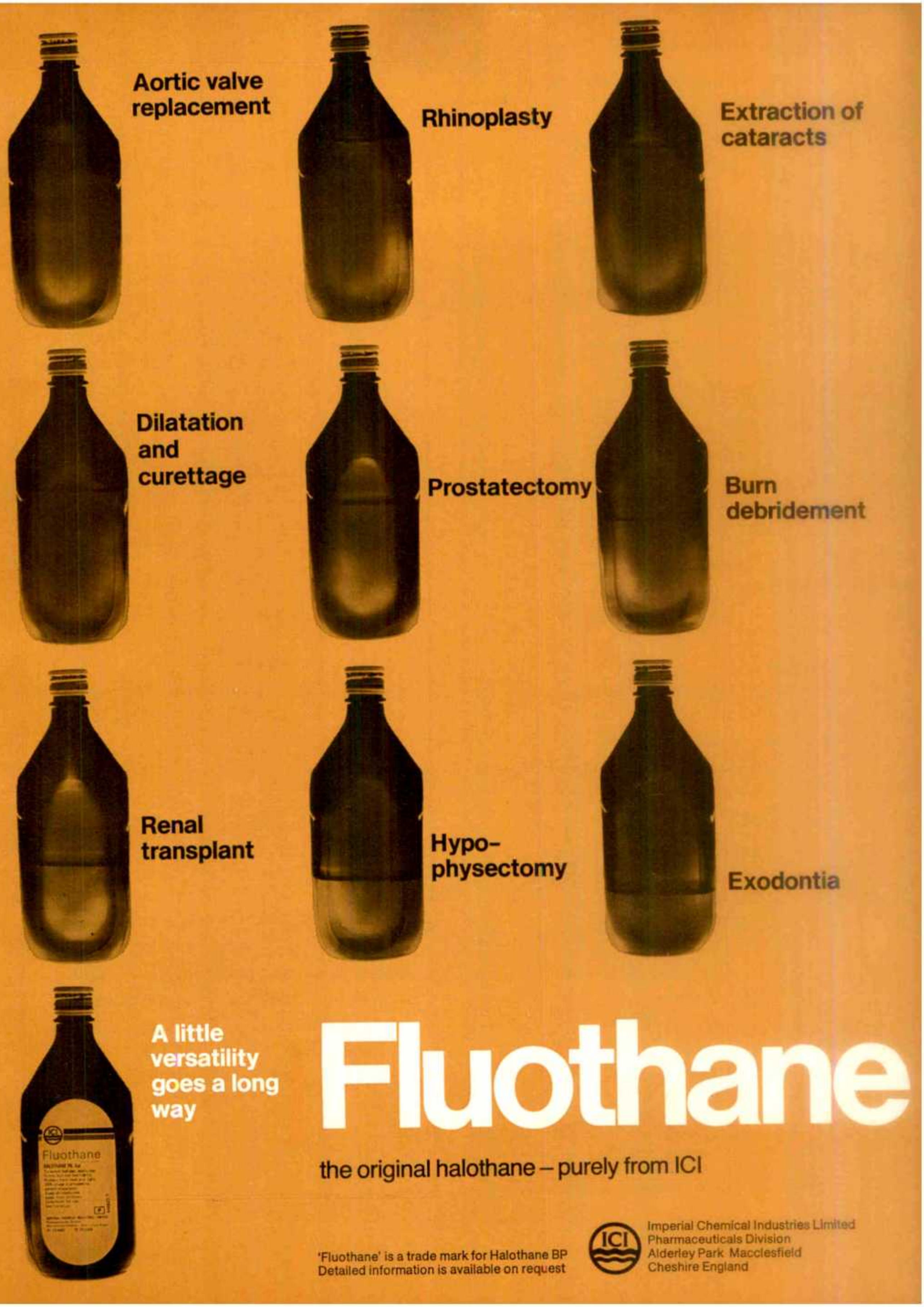

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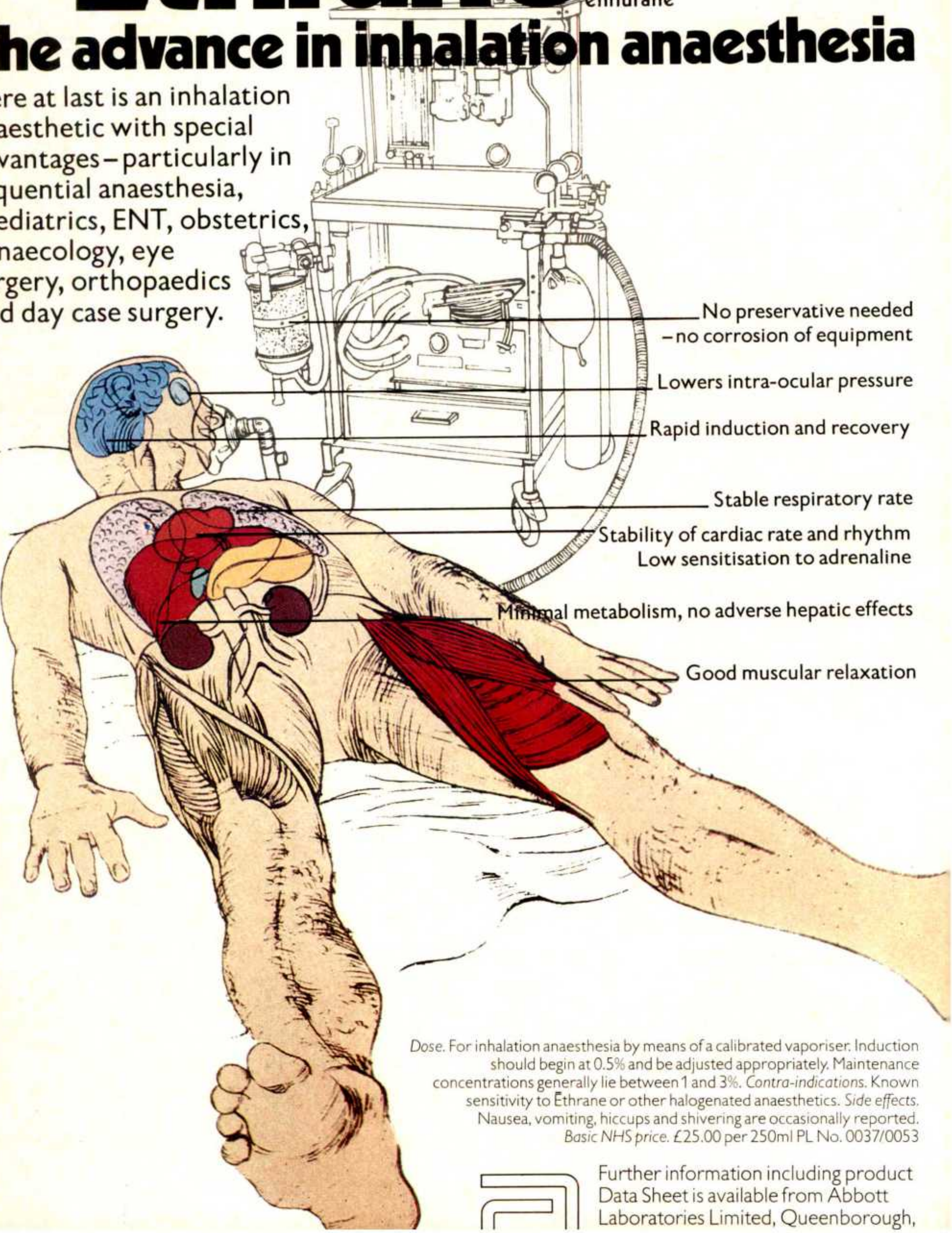
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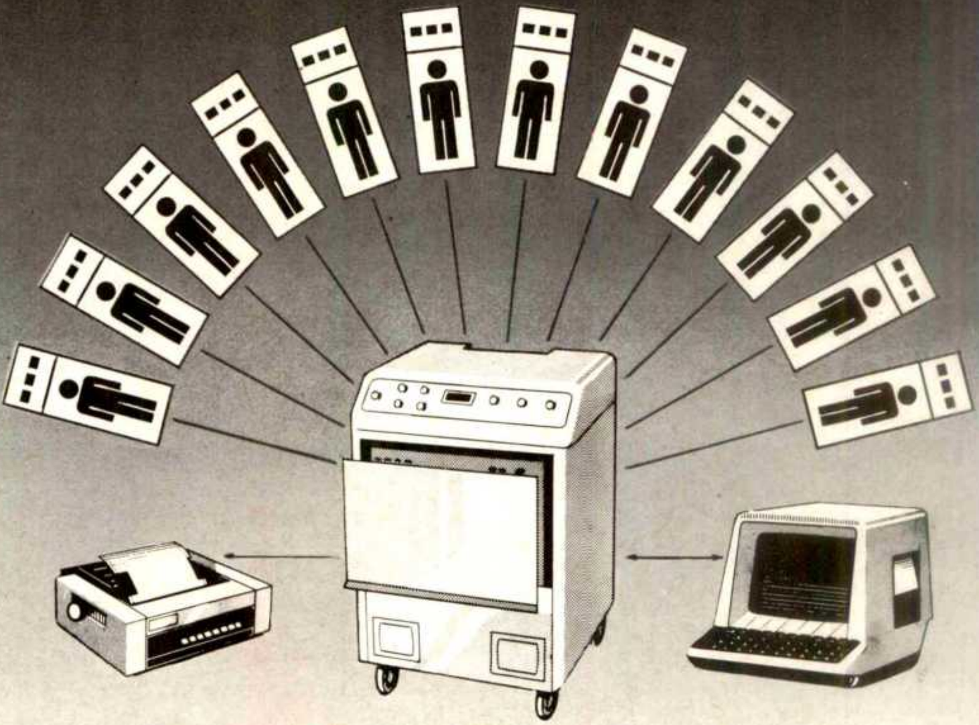

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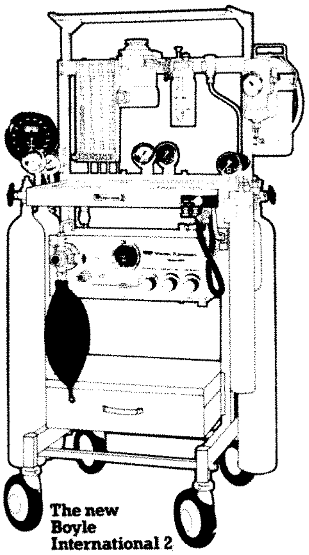

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1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
3. *Postgraduate Medical Journal* (June suppl.) (1972) **48**, 111

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Uses

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Maintenance of anaesthesia

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As usual, it is recommended that patients should fast before receiving Althesin.

The usual intravenous dose of Althesin for both children and adults is between 0·05ml and 0·075ml per kilogram bodyweight, i.e., half to three-quarters of a millilitre per 10kg.

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Althesin has negligible analgesic activity.

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Previous adverse reactions to Althesin.

Hepatic failure

Precautions

Like other anaesthetics, Althesin should only be used in the presence of an experienced anaesthetist, and resuscitative equipment should be immediately available. The risk of severe reactions (see below) may be higher in patients with a personal or family history of atopy. Since Althesin produces relaxation of the jaw muscles, the jaw requires support to prevent obstruction of the airway. Concurrent use of other depressants of the central nervous system may retard recovery of full consciousness, and recovery from anaesthesia should, as always, be assessed carefully before allowing out-patients to go home or resume normal activities. The effects of Althesin are likely to be prolonged in patients with impaired liver function. Animal experiments show no evidence of teratogenicity, but Althesin should be used with caution in pregnancy.

Side effects

Minor side-effects may include a transient flush and muscle twitching, the latter occurring more often in patients given hyoscine alone as premedication. Rarely, clonic contractions may occur. Short periods of coughing, hiccoughing, salivation, laryngospasm or shivering may occur, particularly in association with light anaesthesia or rapid injection.

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Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the author and publishers.

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Two copies of each manuscript should be submitted and should indicate the title of the paper, the name(s), qualifications and full address(es) of the author(s), and be in double-spaced typing on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss.

Papers in recent issues of the *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables
Illustrations

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There should be a separate title page, including the name(s), degrees and address(es) of author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

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Methods

Methods must be described in sufficient detail to allow the experiments to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

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When a drug is first mentioned it should be given the generic or official name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

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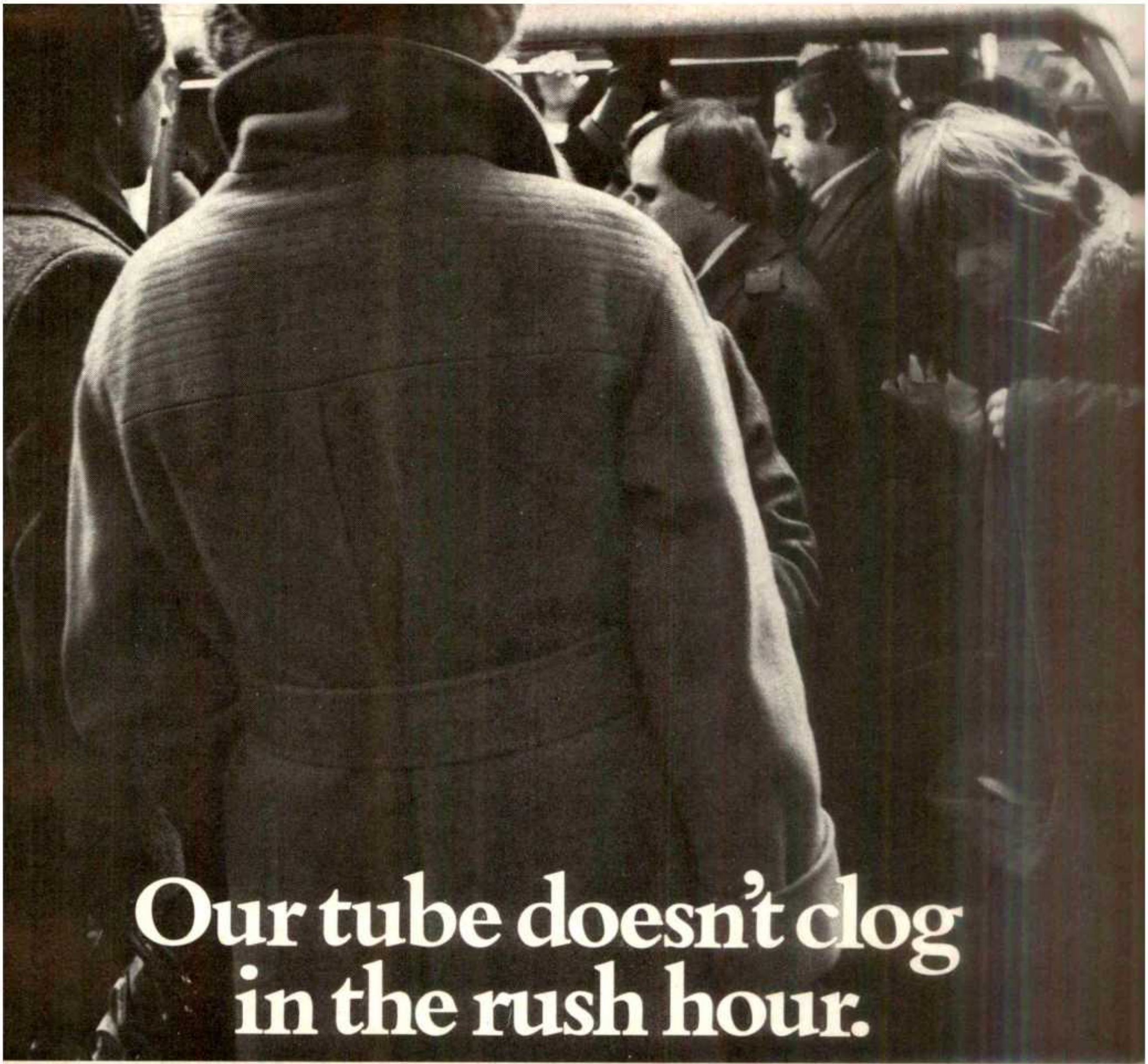

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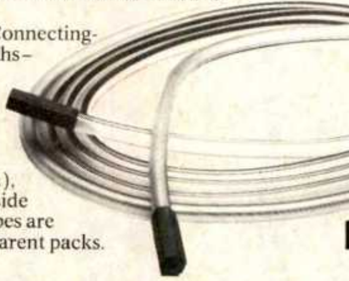

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There should be a table of references at the conclusion of the paper. These references should be arranged according to the Harvard system and in alphabetical order. In the text, the year of publication must follow the author's name, more than one paper in any year being indicated by a small letter (a, b, c,) after the date. In the references, the order should be author's name, followed by initials; year of publication in parentheses; title of paper to which reference is made; title of publication underlined with a single line (to indicate italics) and abbreviated in accordance with *Cumulative Index Medicus*; volume number in arabic numerals, underlined with a wavy line (to indicate bold face); the number of the first page in arabic numbers; thus Clarke, M., Evans, D. W., and Milstein, B. B. (1971). Long-term pacing with an inductive coupling system. *Br. Heart J.*, **33**, 65.

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1) Schneider et al., Chirurg **47,** 185 (1976)
2) McMichan et al., Med. Welt **27,** 2331 (1976)

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1.	PART I	(capitals)
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Spelling, etc. British spelling should be used with "z" rather than "s" spelling in, e.g. organize, organization.

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It is proposed that a proportion of the Journal be devoted to correspondence each month. Every effort will be made to ensure that correspondence arising from papers in a recent issue is published without delay, and for this reason, relevant correspondence will be given priority over that pertaining to original research. Authors of correspondence concerning original work will receive proofs at the Editor's discretion.

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These should be corrected and returned to the sub-editor *within 48 hours of receipt*. Overseas contributors should return their proofs by airmail.

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Extracts from a letter in the Lancet on 21st January 1978 by C. J. Bacon, Department of Child Health, Royal Victoria Infirmary, Newcastle upon Tyne.

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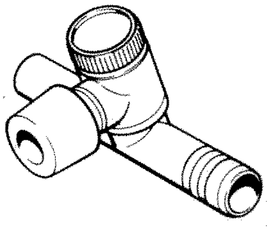

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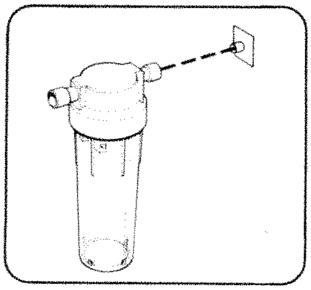

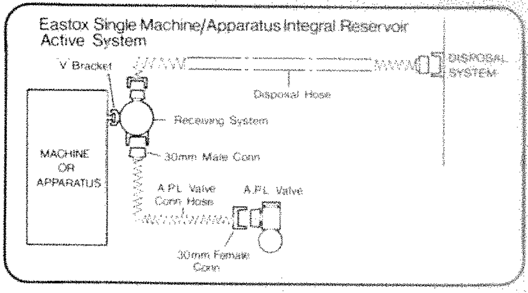

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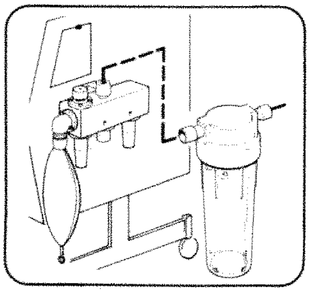

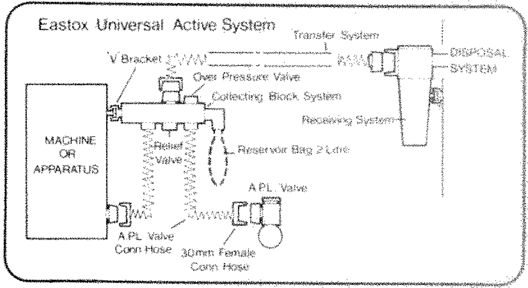

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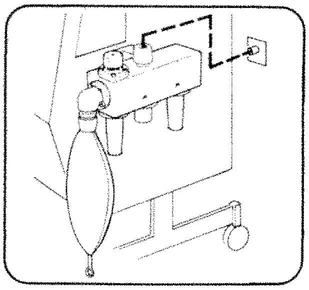

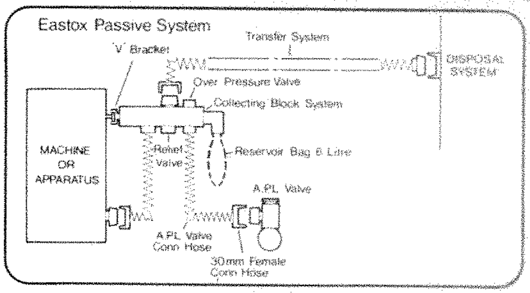

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Indications: Intralipid fat emulsions are indicated in conditions of severe protein depletion requiring also a high energy intake to compensate for excessive loss of calories following trauma, infection, fever, burns, etc.

Dosage and administration Intralipid 10%: 500–1,500 ml daily in conjunction with intravenous amino-acids. For increased caloric requirements Intralipid 20%: 500–1,500 ml daily in conjunction with amino-acids. Intralipid 10% and 20% are administered by slow intravenous infusion. During the first 10 minutes the drip rate should be adjusted to 20 drops per minute and after half an hour this can be adjusted to a final rate of 60 drops per minute. 500 ml of either emulsion should be given in not less than three to five hours on the first day of infusion. On the first day of infusion it is advisable to administer 10 ml Intralipid 10% or 5 ml Intralipid 20% per kg body weight. Subsequently the dose is usually doubled, and when a larger intake is indicated it may be increased to 3 g fat per kg body weight.

Infant dosage: Intralipid 10% or 20%: 15–20 ml per kg body weight in 24 hours.

Contra-indications, warnings, etc. Intralipid is contra-indicated in pathological hyperlipaemia and severe liver damage.

Precautions: When daily intravenous fat administration for more than one week is indicated it must be ascertained, in order to prevent the development of cumulative lipaemia, that the patient is capable of eliminating the infused fat from the circulation, and this function can be tested in the following manner. In the morning following the first day's infusion, a citrated blood sample is drawn, preferably when the patient is still in a fasting state. The blood sample is centrifuged at 1,200–1,500 rpm. If the plasma is then strongly opalescent or milky, further infusion should be postponed. In the great majority of cases, plasma is completely clear 12 hours after the conclusion of an infusion of 2 g fat per kg body weight (corresponding to 20 ml of Intralipid 10% or 10 ml of Intralipid 20% per kg body weight). This test should be repeated at weekly intervals.

Pharmaceutical precautions Store at a temperature between 4°C and 8°C, and do not use after the date of expiry indicated. The contents of each bottle are for a single infusion and any residual emulsion should be discarded. No drugs should be added to Intralipid prior to or during infusion.

Legal category No legal restrictions on sale or supply.

Package quantities *Intralipid 10%:* 100 ml and 500 ml. *Intralipid 20%:* 100 ml and 500 ml.

Further information Nil

Product licence numbers
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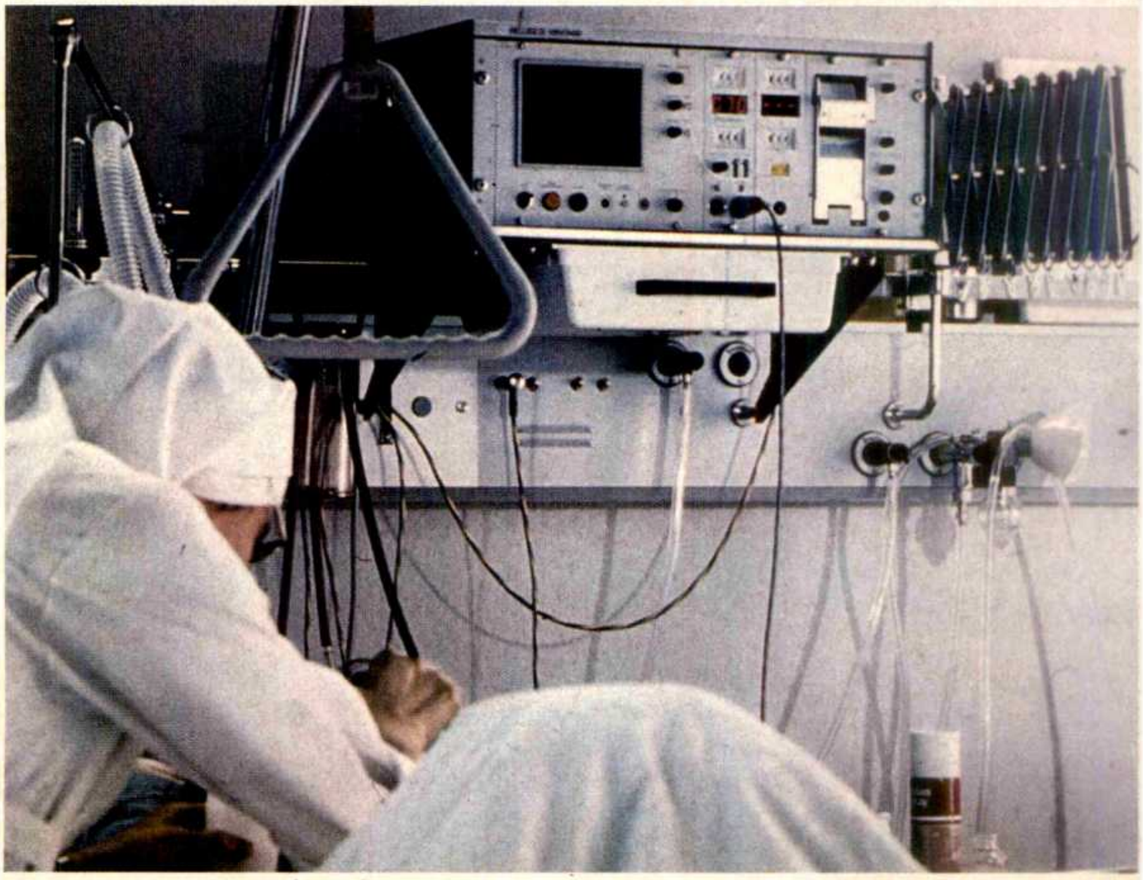

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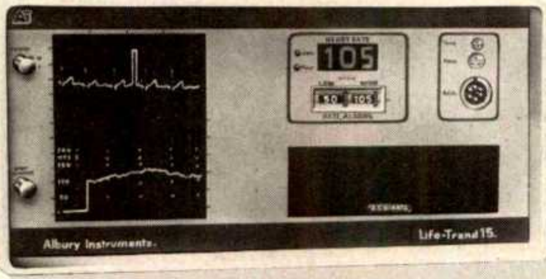

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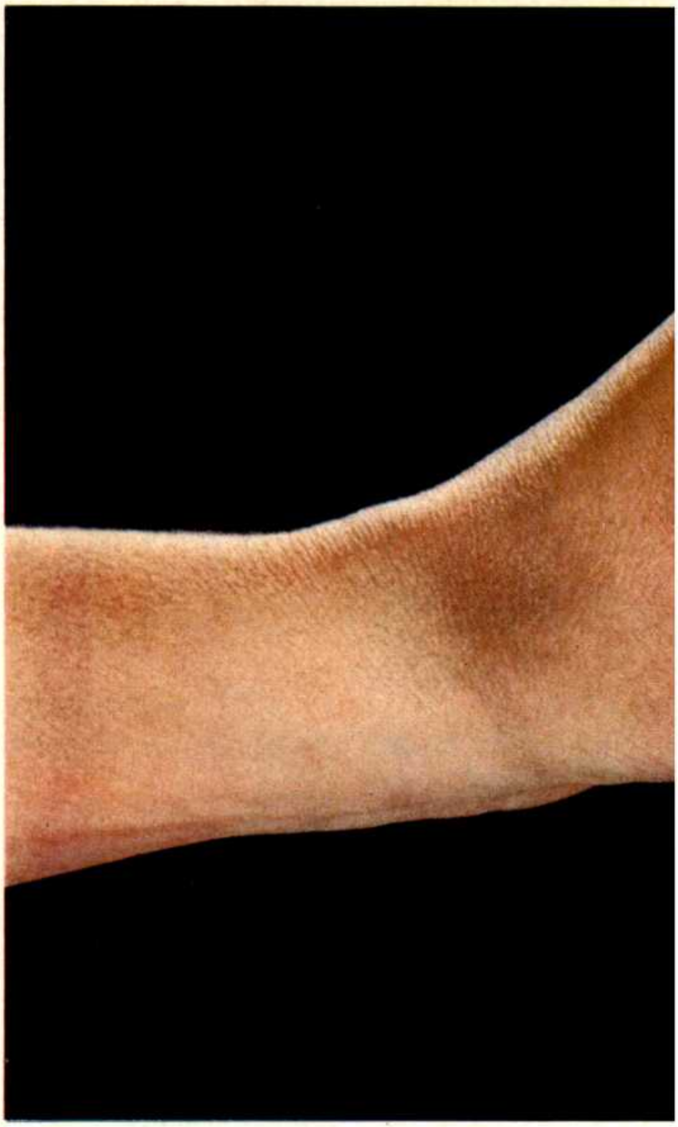

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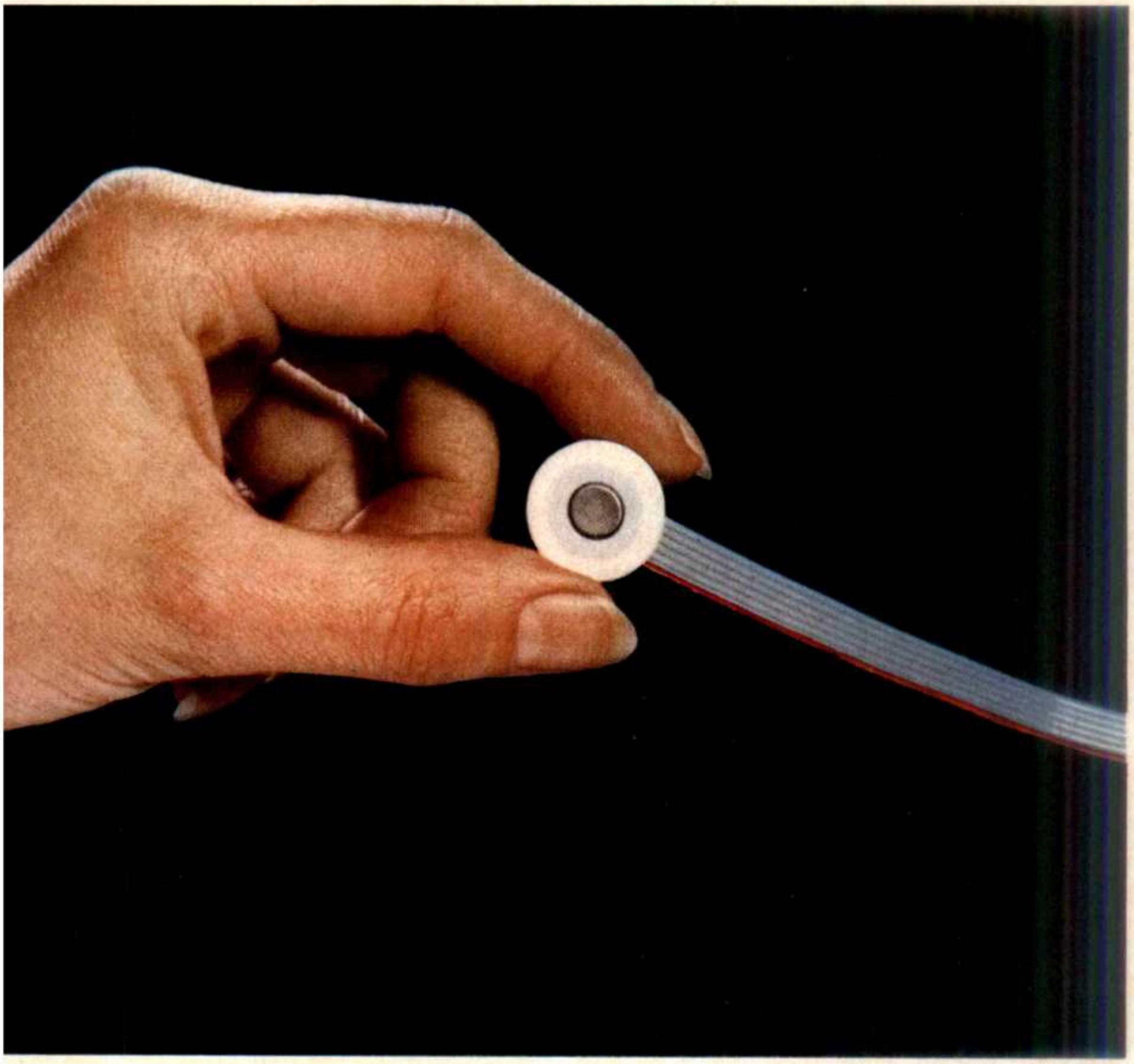

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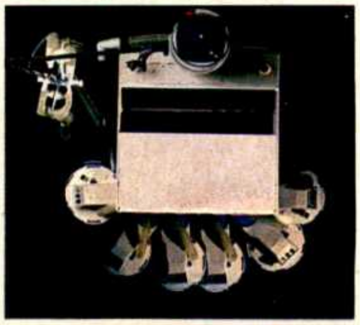

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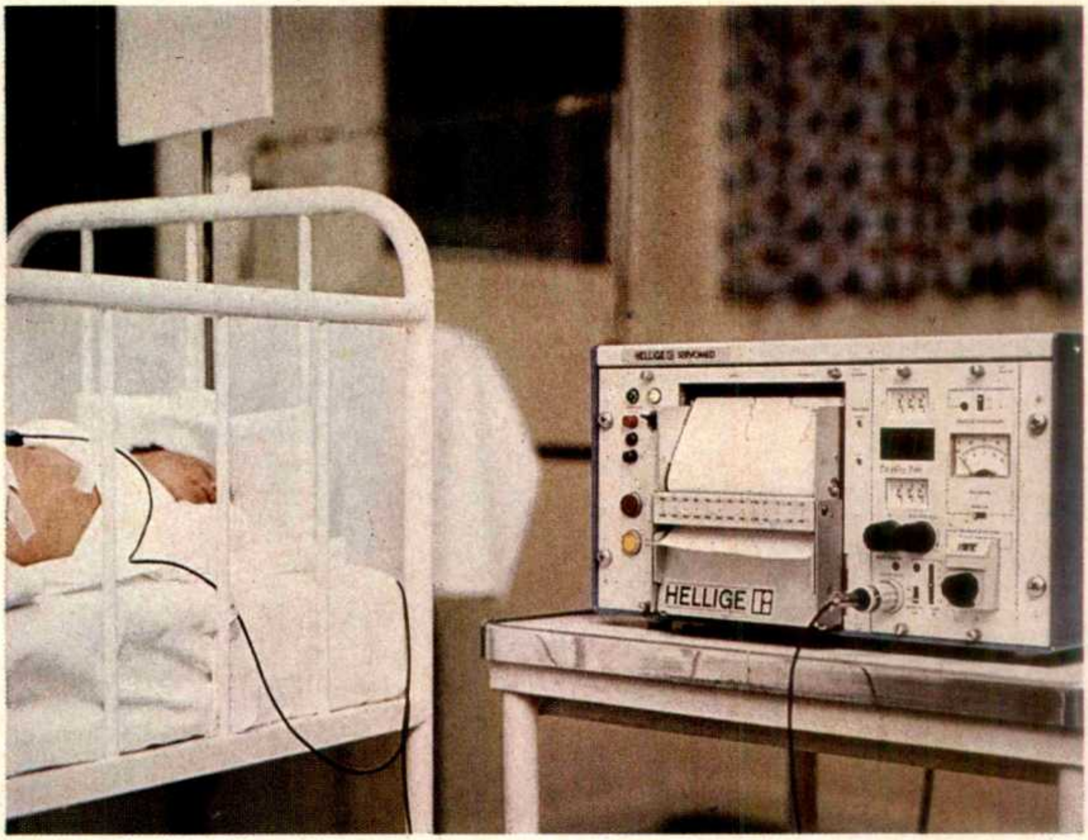

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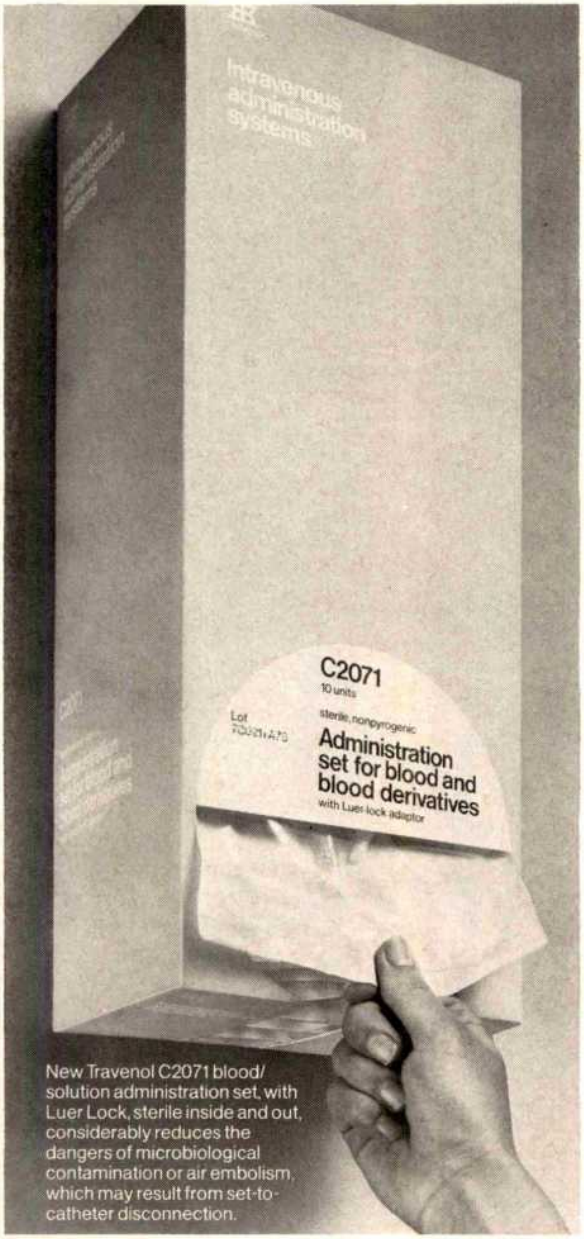
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EDITORIAL

SYMBOLS FOR COMPARTMENTAL MODELS

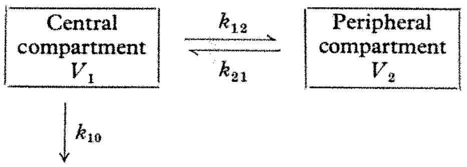
There is no general agreement on the use of symbols in the description of compartmental models and in several instances the variety of usage may have resulted in ambiguity in the past. The proposals described below have been compiled by Dr C. J. Hull, University of Newcastle upon Tyne, and British Journal of Anaesthesia *proposes to conform to this system in future.*

The compartmental model has become a popular analytical tool in pharmacological research. It depends heavily upon an explicit notation, but unfortunately there is little in common between the systems of symbols used by different groups of workers. In particular, the notation of rate constants is in urgent need of standardization, because the symbols adopted by some authors are in direct conflict with those of others (table I).

It is proposed that we adopt a *rational* system of symbols, similar to those devised for respiratory physiology (Pappenheimer and Committee, 1950).

TABLE I. *Variation in nomenclature for the rate constants of a 2-compartment "open" model*

Two-compartment model



	k_{12}	k_{21}	k_{10}
Atkins (1969)	k_{21}	k_{12}	k_{01}
Gibaldi and Perrier (1975)	k_{12}	k_{21}	k_{10}
Hull and McLeod (1976)	K_{AB}	K_{BA}	K_{EL}
McLeod, Rawlins and Watson (1976)	k_{12}	k_{21}	k_{13}
Saunders (1978)	k_1	k_2	k_e
Wagner (1971)	k_{12}	k_{21}	k_{el}
Wagner and others (1968)	K_1	K_{-1}	K_2

General variables, such as concentration and amount of drug, are given capital italic letters, followed if required by a lower case letter to specify the *nature* of the variable. First order rate constants are indicated by k, zero order constants by k' and time by t (except in the case of half-life, which by S.I. convention is given the symbol $T_{\frac{1}{2}}$). K should be reserved for equilibrium constants. Since volume is denoted by V, clearance (which has the dimension of flow) could logically be given the first derivative symbol $\dot{V}$. It must, however, be conceded that *Cl* has achieved wide acceptance among pharmacokineticists. Since the purpose of this proposal is to promote conformity, we suggest that clearance be denoted by *Cl*.

The variable or rate constant may be followed by a subscript of numerals or *small* capitals, indicating the *location*, and a superscript indicating *time* conditions. In the unlikely event of an author wishing to raise a symbol to a *power*, the symbol should be first put in parentheses, to avoid confusion with symbolic superscripts.

Using this system of symbols (table II) most of the quantities required for compartmental analysis can be specified. Those which cannot should be allotted special symbols, in accord with the general principles of the system. They should be defined at the beginning of each publication.

Volume and amount of drug are defined in litre and mol respectively. Authors using this system of notation may assume that these definitions apply, provided that they refer to this editorial.

TABLE II.

General variables	
X	Amount of drug at time t (mol)
V	Apparent volume (litre)
C	Concentration of drug at time t (mol litre^{-1})
F	Fraction of dose available for absorption
Cl	Clearance (litre per unit time)
Q	Blood flow (litre per unit time)
t	Time (seconds, minutes, or hours)
$T_{\frac{1}{2}}$	Half-life (seconds, minutes or hours)
Qualifying letters after variable (lower case)	
m	Metabolite
b	Bound drug
f	Free drug
d	Dose given as bolus
Constants	
k	First order rate constant (h^{-1})
k'	Zero order rate constant (mol h^{-1})
K	Equilibrium constant
Subscripts to indicate location (small capitals or numerals)	
1, 2, 3, . ., 9	Compartmental labels
0	Exterior (compartment zero)
31	Paired numbers indicate drug moving from compartment 3 *to* compartment 1
1–12	In the event of a compartmental number exceeding 9, rate constant subscripts are clarified by a hyphen
A	Absorption site
R	Renal
H	Hepatic
P	Plasma
Superscripts to indicate time conditions	
ss	Steady state
0	Time zero
tot	Total period of measurement
α, β, γ, etc.	During specific exponential phases

To illustrate the wide application of this system of notation, a number of commonly used quantities are listed:

C_1	Concentration of drug in compartment 1 at time t (mol litre^{-1})
C_2	Concentration of drug in compartment 2 at time t (mol litre^{-1})
C_2^0	Concentration of drug in compartment 2 at time 0 (mol litre^{-1})
C_1^{ss}	Concentration of drug in compartment 1 at steady state (mol litre^{-1})
X	Amount of drug in body at time t (mol)
Xm	Amount of metabolite in body at time t (mol)
X_A	Amount of drug in the absorption site at time t (mol)
Xd	Amount of drug given as a bolus dose (mol)
Xd^{tot}	Total amount of drug given in all doses (mol)
X^{ss}	Amount of drug in the body at steady state (mol)
X_1^{ss}	Amount of drug in compartment 1 at steady state (mol)
V	Apparent volume of distribution of a 1-compartment model (litre)
V^{β}	Apparent volume of distribution during β phase (litre)
V^{ss}	Apparent steady state distribution volume (litre)
V_2	Apparent volume of compartment 2 in an n-compartment model (litre)
t	Time (seconds, minutes or hours, defined by the author)
$T_{\frac{1}{2}}$	Half-life (same units as t)
$T_{\frac{1}{2}}^{\alpha}$	Half-life of the initial rapid exponential term
Cl	Whole body drug clearance (litre per unit time)
Clm	Whole body metabolite clearance (litre per unit time)
Cl_1	Clearance of drug from compartment 1 (litre per unit time)
Cl_P	Plasma clearance (litre per unit time)
k'_{10}	Apparent zero order elimination rate constant from compartment 1 (mol h^{-1})
k'_{01}	Zero order *infusion* rate constant into compartment 1 (mol h^{-1})
k_{A1}	Apparent first order absorption rate constant into compartment 1 (h^{-1})
k_{12}	Apparent first order rate constant from compartment 1 to compartment 2 (h^{-1})
k_{20}	Apparent first order elimination rate constant from compartment 2 (h^{-1})

Examples of some commonly used formulae:

(1) In an n-compartment model, the steady-state distribution volume V^{ss} is defined as

$$V^{ss} = V_1\left[1+\frac{k_{12}}{k_{21}}+\frac{k_{13}}{k_{31}}\dots+\frac{k_{1n}}{k_{n1}}\right]$$

(2) During the elimination phase, the apparent distribution volume of a 2-compartment model is defined as

$$V^{\beta} = \frac{V_1 . k_{10}}{\beta}$$

(3) At a constant infusion rate, the drug concentration in a 1-compartment model increases according to

$$C = \frac{k'_{01}}{V . k_{10}}\left[1-\exp\left(-k_{10} . t\right)\right]$$

and at steady state

$$C^{ss} = \frac{k'_{01}}{V.k_{10}}$$

Since clearance is the product $V.k_{10}$, this equation can be further simplified to

$$C^{ss} = \frac{k'_{01}}{Cl}$$

(4) Similarly, the concentration in the central compartment of a 2-compartment model increases with infusion according to

$$C_1 = \frac{k'_{01}}{V_1.k_{10}}\left[1+\frac{\beta-k_{10}}{\alpha-\beta}\exp(-\alpha t) + \frac{k_{10}-\alpha}{\alpha-\beta}\exp(-\beta t)\right]$$

As in the 1-compartment model, this reduces at steady state to a simple expression:

$$C^{ss} = \frac{k'_{01}}{Cl_1}$$

To achieve a specified steady state concentration C^{ss} the infusion rate must be

$$k_{01} = C^{ss}.V_1.k_{10}$$

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AN ANIMAL MODEL FOR THE INVESTIGATION OF ADVERSE RESPONSES TO I.V. ANAESTHETIC AGENTS AND THEIR SOLVENTS

J. B. GLEN, G. E. DAVIES, D. S. THOMSON, S. C. SCARTH AND A. V. THOMPSON

SUMMARY

In man the number of adverse responses to the Cremophor-containing anaesthetic agents Althesin and propanidid (Epontol) has been reported to be greater than that encountered with thiopentone. The response of the mini-pig to repeated injection of a range of i.v. anaesthetics and their solvents has been investigated in an attempt to ascertain the possible role of Cremophor in the production of these responses. A second injection of Cremophor EL or the Cremophor/Micellophor-containing agents Althesin and propanidid (Epontol), given 7 days after the first, produced a high frequency of adverse responses. On only one occasion, when alphaxalone and alphadolone were given in a mixture of alcohol and propylene glycol, was an abnormal response seen on the first administration of any agent. The second administration of alphaxalone and alphadolone in the same solvent produced abnormal responses in two of four pigs. No such responses were seen when propanidid was administered in alcohol and propylene glycol or when this solvent mixture was given alone. No abnormal responses were seen following the repeated administration of thiopentone. A marked increase in arterial pressure, and an immediate but transient marked decrease in the numbers of circulating polymorphonuclear leucocytes, were consistent findings in animals showing adverse responses. No abnormal responses were found when the interval between two administrations of Althesin was extended to 3 weeks.

It has been shown that injection of the i.v. anaesthetic agents thiopentone, propanidid and Althesin can produce histamine release in man (Lorenz et al., 1972; Doenicke et al., 1973). The amount of histamine released is normally insufficient to be of any clinical significance. These authors were unable to demonstrate histamine release in man following the administration of the hypnotic agent etomidate or the solubilizing agent Cremophor EL.

Our original aim was to find an animal model with which to evaluate the histamine-releasing propensity of potential new anaesthetic agents. The pig resembles man in being insensitive to the histamine-releasing properties of Cremophor EL (Lorenz et al., 1971) and was selected as a suitable species in which to evaluate the effects of Cremophor-containing anaesthetics. The dog could not be used since the injection of Cremophor almost invariably produces a massive release of histamine.

Preliminary studies in pigs failed to demonstrate any significant increase in plasma histamine concentrations following a single injection of Althesin. At this time, the finding by Watkins, Clark and others (1976) of a high frequency of subclinical "hypersensitivity" reactions in man, following single and repeated injections of Althesin, propanidid and methohexitone, prompted us to examine the effect of repeated doses of Althesin in the pig. The reactions in man were characterized by significant changes in white cell counts. In our early studies in pigs we found that the repeated administration of Althesin produced a rapid and marked reduction in the number of circulating polymorphonuclear leucocytes and that this effect was accompanied by an abnormal clinical response (Glen et al., 1978). This work has now been extended to an examination of the effects of repeated injections of a range of Cremophor-containing and Cremophor-free anaesthetics and their solvents. We hoped to assess the importance of the solvent in the production of adverse responses with the aim of developing an animal model which could be used to evaluate potential alternative solubilizing agents.

METHODS

Mini-pigs (Göttingen derived strain) of both sexes (weight 12–20 kg) were studied. One week before the first administration of a test agent, carotid and jugular cannulae were implanted to allow arterial pressure

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J. B. GLEN, B.V.M.S., M.R.C.V.S., D.V.A.; G. E. DAVIES,* B.SC., D.SC., F.P.S., F.I.BIOL.; D. S. THOMSON, F.I.M.L.S.; S. C. SCARTH; A. V. THOMPSON*; Biology Department, I.C.I. Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire.

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to be measured and to facilitate the administration of test agents and the withdrawal of blood samples. For this procedure pigs were sedated with droperidol and anaesthesia was induced and maintained with halothane. Arterial pressure was measured before and during the period of anaesthesia and recovery with a Bell and Howell strain gauge transducer. Heart rate was derived electronically from the arterial pressure input and records of both measurements were obtained on a Devices M19 recorder. Samples of arterial blood were collected before the administration of a test agent and at 2, 5, 10 and 20 min after injection. Arterial pH, $P\text{O}_2$ and $P\text{CO}_2$ were measured in heparinized blood samples using standard Radiometer or Corning electrodes. Samples for plasma histamine measurement were collected into EDTA and centrifuged at 1500 *g* for 60 min. An equal volume of trichloroacetic acid was added to the supernatant, to precipitate protein, and plasma histamine concentration was measured using an automated fluorimetric assay (Evans, Lewis and Thomson, 1973). Total and differential white cell counts were performed by standard methods. Rectal temperature was measured during anaesthesia with a mercury thermometer. Abnormal clinical responses and sleeping times to head-lift were noted.

The doses of the anaesthetic agents investigated were thiopentone 10 mg kg^{-1}, alphaxalone/alphadolone 0.15 ml kg^{-1} (1.8 mg kg^{-1} total steroids) and propanidid 10 mg kg^{-1}. These are the minimum doses required to produce unconsciousness in the mini-pig. In addition to Cremophor EL, an alternative solvent system containing 10% ethyl alcohol and 25% propylene glycol was examined. This allowed a comparison to be made of the effects of Cremophor-free preparations of alphaxalone/alphadolone and propanidid with those of the commercially available Cremophor- and Micellophor*-containing preparations, Althesin (Glaxo) and Epontol (Bayer) respectively. Solvents, when examined alone, were given in a volume and concentration equal to that contained in the anaesthetic formulations. All injections were given over 30 s.

In most instances an interval of 1 week was allowed between the administration of two doses of a test agent. Additional experiments were performed with Althesin using intervals of 4, 14 and 21 days, and Cremophor was also readministered after a 14-day interval. Different groups of pigs were used for each agent or interval examined. Thus each pig received only two injections of the same agent.

The significance of differences occurring within an experiment was estimated with a paired Student's *t* test.

RESULTS

The results obtained in the first series of experiments where a 1-week interval was allowed between the administration of two doses of a test agent are summarized in table I.

Abnormal clinical responses

Cremophor EL and the Cremophor- and Micellophor-containing agents Althesin and Epontol all produce frequent reactions when a second administration was given 7 days after the first exposure. On only one occasion, when alphaxalone and alphadolone

TABLE I. *Responses obtained in mini-pigs on the second administration of anaesthetic agents and solvents, 7 days after an initial exposure. *Althesin (Glaxo) contains alphaxalone and alphadolone; †Epontol (Bayer) contains propanidid*

Anaesthetic agent	Solvent	No. of pigs	Abnormal clinical response	Hypertensive response >50 mm Hg	Decrease in polymorph count >50%	Increase in Plasma histamine >50%
Thiopentone	Water	6	0	0	0	2
Althesin*	20% Cremophor EL	4	3	3	3	2
Epontol†	20% Micellophor	6	5	5	6	3
Alphaxalone/ alphadolone	10% ethyl alcohol/ 25% propylene glycol	4	2	3	1	1
Propanidid	10% ethyl alcohol/ 25% propylene glycol	4	0	0	0	0
	20% Cremophor EL	5	4	5	5	4
	10% ethyl alcohol/ 25% propylene glycol	3	0	0	0	0

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* Micellophor is a butanol extract of Cremophor and contains the same hydrophobic constituents.

were given in alcohol and propylene glycol, was an abnormal response seen on the first administration of any agent. The second administration of alphaxalone and alphadolone in the same solvent produced abnormal clinical responses in two of four pigs. No such responses were seen when propanidid was administered in alcohol and propylene glycol or when this solvent mixture was given alone. No abnormal responses were seen following the repeated administration of thiopentone.

Pigs showing an abnormal response developed an initial cutaneous hyperaemia and frequently showed convulsive limb and head movements. Peripheral cyanosis or a transient urticarial rash appeared later. The responses produced by different agents were generally similar. Convulsive kicking and peripheral cyanosis were noted most frequently in the animals receiving Cremophor EL or Epontol, while the overt signs of a response were less marked following administration of the alphaxalone/alphadolone mixture in the alternative solvent. Three of the pigs which responded to Cremophor became unable to stand for a short period, salivated excessively and vomited. Rectal temperature did not change significantly during any of the reactions. No treatment or supportive therapy was given and all animals survived.

Sleeping times

Mean sleeping times on both exposures for each group of pigs are given in table II. Pigs receiving a second injection of Althesin or alphaxalone/alphadolone in the alternative solvent slept for a longer period than that found on the first exposure to these agents, but the difference was not statistically significant.

Respiratory effects

In pigs showing an abnormal response a period of apnoea of 20–60 s was seen frequently following the administration of a test agent. On other occasions a brief period of irregular respiration or coughing was noted. Respiratory depression appeared to be central in origin and not associated with bronchospasm. Changes in arterial Po_2 and Pco_2 are shown in figure 1, in which it can be seen that Po_2 decreased slightly in the groups receiving the anaesthetic agents, but was virtually unchanged at 2 min in the group responding to a second injection of Cremophor. Only in the animals given alphaxalone/alphadolone in the alternative solvent was the decrease statistically significant ($P < 0.01$). Later, when peripheral cyanosis was frequently evident, arterial oxygenation had returned to normal in the groups which received the anaesthetic agents. Arterial Pco_2 values were not altered significantly and the changes in pH did not indicate any effect on metabolic acid–base status.

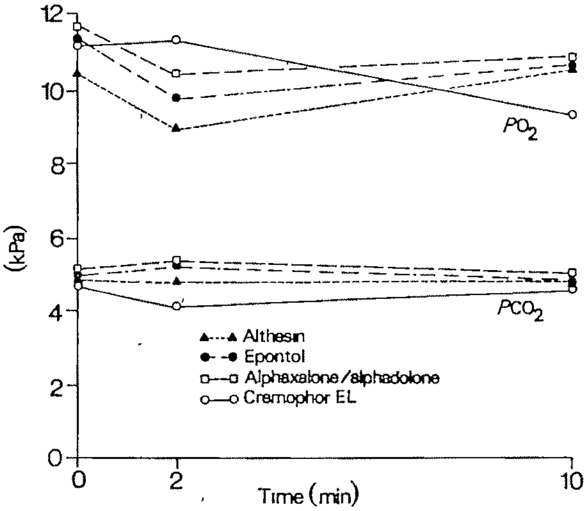

FIG. 1. Changes in arterial Po_2 and Pco_2 in pigs showing abnormal clinical responses.

In animals given thiopentone, or propanidid in the alternative solvent, the decrease in Po_2 2 min after

TABLE II. *Sleeping times produced by two administrations of a range of i.v. anaesthetic agents*

Anaesthetic agent	No. in group	No. of responders on day 8	Mean (±SD) sleeping time to head-lift (min) Day 1	Day 8
Thiopentone	6	0	10.0±3.4	10.3±3.7
Althesin	4	3	6.5±1.2	13.5±5.9
Epontol	6	5	2.9±1.1	3.5±3.3
Alphaxalone/alphadolone	4	2	7.1±2.3	10.6±4.1
Propanidid	4	0	4.0±0.8	4.5±0.57

injection was similar to that seen in pigs showing an adverse response to one of the other anaesthetic formulations.

Plasma histamine concentrations

Plasma histamine concentration was not invariably increased in pigs showing an abnormal clinical response (table I). Increases were found most consistently in pigs given Cremophor or propanidid. Despite the finding of large concentrations—106 ng ml^{-1} and 135 ng ml^{-1} at 2 min in individual pigs in the groups given Cremophor and Epontol respectively—none of the increases was statistically significant. The mean plasma histamine concentrations found in pigs showing abnormal clinical responses are given in figure 2. In one pig which showed an abnormal response to a second injection of alphaxalone and alphadolone in the alternative solvent, plasma histamine concentration increased from 40 ng ml^{-1} to 84 ng ml^{-1}. The increase noted in two pigs given a second injection of thiopentone was not associated with any other sign of an abnormal response.

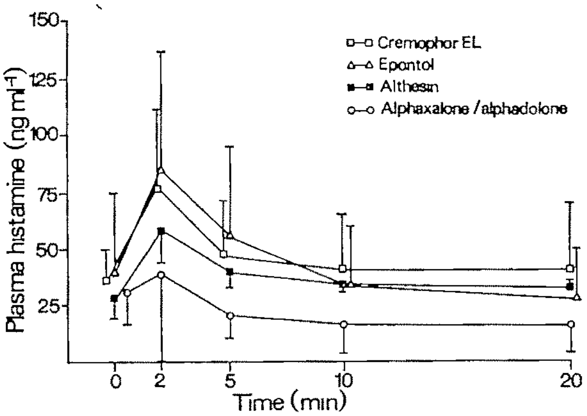

FIG. 2. Plasma histamine concentrations in pigs showing abnormal clinical responses.

Haemodynamic effects

In all animals in which an abnormal clinical response was noted, and on two occasions when no clinical signs indicating an abnormal response were seen, a marked hypertensive response developed a few seconds after the administration of the test agents. Maximum mean arterial pressures in the groups showing abnormal reactions are given in table III. Maximum values were reached within 1 min and thereafter mean pressure returned to pre-dose values over the succeeding 5–10 min. The maximum values reached in all groups were similar. A typical record illustrating these changes is shown in figure 3. In this animal the first administration of Epontol produced only a brief depressor effect, whereas the second injection, given 7 days later, produced a marked pressor response. On only one occasion was a similar pressor response noted on the first administration of a test agent. The record obtained from this animal,

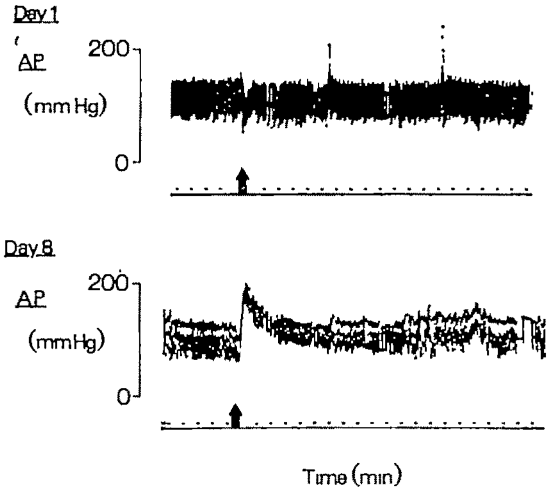

FIG. 3. The effect of repeated injection of Epontol on arterial pressure in a mini-pig.

TABLE III. *Hypertensive responses in pigs showing abnormal clinical responses. *One animal which responded abnormally on day 1 is included in this group*

Anaesthetic or solubilizing agent	n	Arterial pressure (mean ± SD) (mm Hg)		
		Pre-dose	Maximum recorded	P
Althesin	3	103.7 ± 7.23	197.7 ± 7.93	< 0.001
Epontol	5	103.0 ± 18.4	180.8 ± 21.4	< 0.001
Alphaxalone/ Alphadolone	3*	106.3 ± 11.01	192.3 ± 21.5	< 0.05
Cremophor EL	4	107.2 ± 8.99	205.5 ± 10.4	< 0.01

which was given alphaxalone/alphadolone in alcohol and propylene glycol, is shown in figure 4.

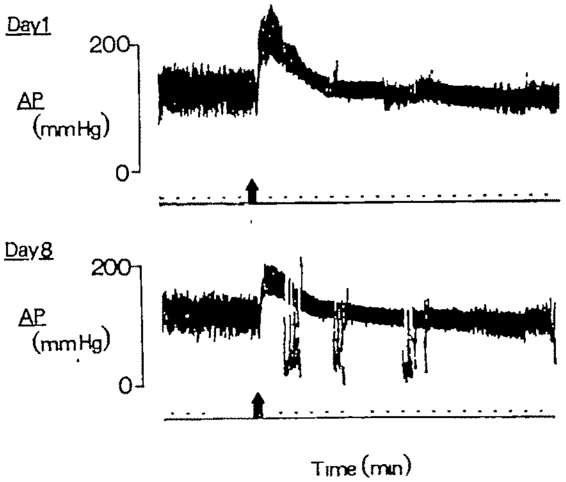

FIG. 4. The effect of repeated injection of alphaxalone/alphadolone, solubilized in alcohol and propylene glycol, on arterial pressure in a mini-pig. Artefacts on lower trace were produced by blood sample collection.

Heart rate increased as the pressor effect was initiated, but in many instances reflex bradycardia occurred when the hypertensive response was fully developed. Pulse pressure was frequently reduced about 5 min after drug administration and at this time a peripheral pulse could not be readily detected.

The increase in arterial pressure usually preceded any overt signs of an adverse response and it is possible that this very rapid and marked increase may have been responsible for some of the convulsive signs and apnoea noted in the early stages of a reaction.

Effects on white blood cells

In one pig in which an abnormal clinical response was noted following the first injection of alphaxalone/alphadolone in alcohol and propylene glycol, the polymorph count decreased from a value before injection of 9.03 × 10^9 litre^{-1} to 4.4 × 10^9 litre^{-1} 2 min after injection. No significant changes in total or differential white cell counts occurred in any other pig following the first administration of a test agent.

A typical finding in pigs showing an adverse response to a second administration of a test agent was the virtual disappearance of polymorphonuclear lymphocytes in blood samples collected 2 and 5 min after injection. This decrease in polymorph count was reflected in the total white cell count. Lymphocyte numbers were not significantly altered (fig. 5). The mean changes in polymorph count 2 min after the second administration of each test substance are given in table IV. It can be seen that Althesin, Epontol,

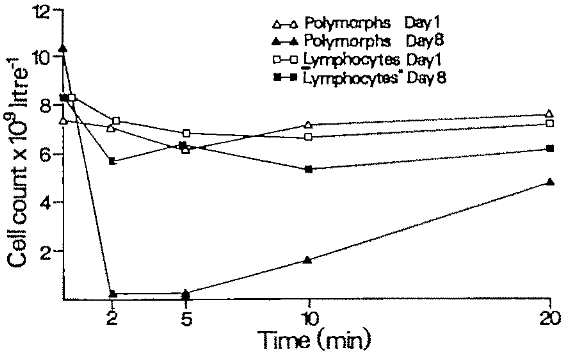

FIG. 5. Polymorph and lymphocyte counts in pigs responding to a second injection of Cremophor 7 days after an initial exposure.

TABLE IV. *Changes in polymorph count in mini-pigs on the repeated administration of anaesthetic agents and solvents, 7 days after an initial exposure*

Anaesthetic agent	Solvent	No. of pigs	No. showing abnormal clinical response	Polymorph count × 10^9 litre^{-1} (mean ± SD) Before injection	2 min after injection	P	%Δ
Thiopentone	Water	6	0	9.06 ± 2.55	8.96 ± 3.72	n.s.	−1.1
Althesin	20% Cremophor EL	4	3	6.90 ± 3.32	1.33 ± 1.41	n.s.	−80.7
Epontol	20% Micellophor	6	5	7.49 ± 3.76	0.49 ± 0.61	< 0.01	−93.5
Alphaxalone/ alphadolone	10% ethyl alcohol/ 25% propylene glycol	4	2	11.6 ± 7.33	6.53 ± 4.87	< 0.05	−43.7
Propanidid	10% ethyl alcohol/ 25% propylene glycol	4	0	6.92 ± 2.22	6.66 ± 2.20	n.s.	−3.8
	20% Cremophor EL	5	4	10.94 ± 4.01	0.76 ± 1.41	< 0.01	−93.1
	10% ethyl alcohol/ 25% propylene glycol	3	0	7.51 ± 2.05	8.77 ± 4.26	n.s.	+16.8

alphaxalone/alphadolone in alcohol and propylene glycol, and Cremophor all produced marked changes at this time whereas thiopentone, propanidid in alcohol and propylene glycol, and this latter solvent mixture on its own, produced only minor effects. The time course of these changes in polymorph count in animals, in which adverse clinical responses were noted, is depicted in figure 6.

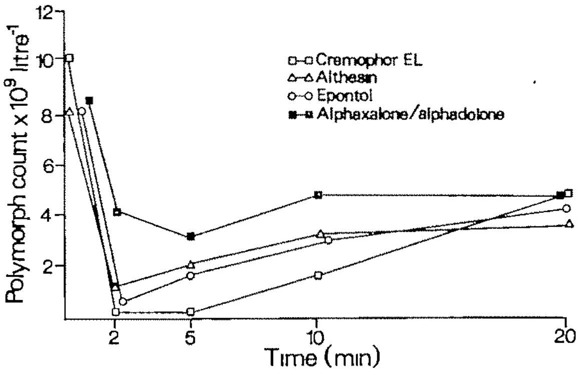

FIG. 6. Polymorph counts in pigs showing abnormal clinical responses.

Effect of varying the interval between injections

The results are summarized in table V, in which it can be seen that a high frequency of adverse responses to Althesin occurred when a second injection was given after 1 or 2 weeks, whereas only one mild reaction was produced when the interval between two injections was 4 days or 3 weeks. Adverse responses to Cremophor EL were noted less frequently when the interval between two injections was extended from 1 to 2 weeks. The changes in polymorph count, at different times of challenge (figs 7, 8), reflected the changes in clinical responses. This suggests that sensitivity to Cremophor EL may possibly be lost more rapidly than that to Althesin.

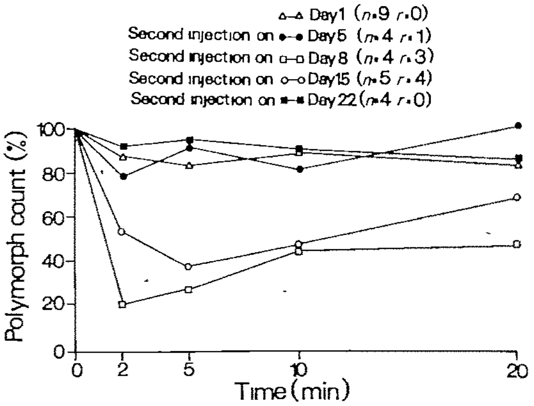

FIG. 7. Polymorph counts in pigs given Althesin on day 1, and after an interval of 4, 7, 14 or 21 days. n = number of pigs in which differential white cell counts were performed: r = number of pigs showing an adverse clinical response.

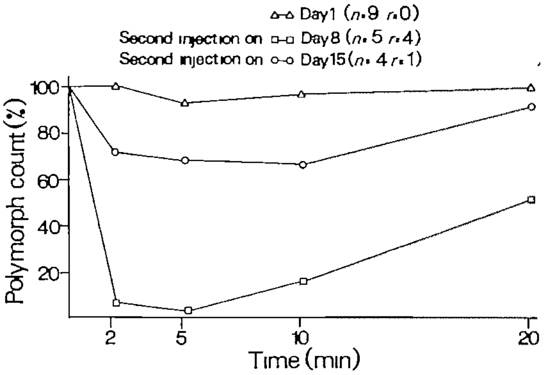

FIG. 8. Polymorph counts in pigs given Cremophor on day 1 and after an interval of 7 or 14 days.

DISCUSSION

Of the i.v. anaesthetic agents currently in use the greatest frequency of adverse responses in man has been found to be associated with Althesin (Clark et al.,

TABLE V. *Adverse responses to Althesin and Cremophor with various intervals between injections*

Interval between injections (days)	No. of pigs	Abnormal clinical response	Hypertensive response >50 mm Hg	Reduction in polymorph count >50%	Increase in plasma histamine >50%
Althesin					
4	4	1	0	0	0
7	4	3	3	3	2
14	5	3	3	3	2
21	4	0	0	0	0
Cremophor					
7	5	4	5	5	4
14	4	1	1	0	0

1975). These authors estimated the frequency of reactions to this agent to be between one in 11 000 and one in 19 000. A larger figure of about one in 1000 was obtained in a smaller, retrospective study by Evans and Keogh (1977). The extremely high frequency of reactions produced in the pig in the present study indicates that this species is particularly sensitive to the repeated administration of agents which have been known to produce reactions in man. We have been unable to produce any similar response in mice, guineapigs, rats or rabbits following the repeated administration of Althesin or Cremophor.

The responses noted in pigs differed from those associated with adverse reactions in man in that bronchospasm was not a feature of the reaction in the pig and marked hypertension rather than hypotension was a consistent finding. On the other hand, the cutaneous effects, the involvement of histamine release in some of the reactions, and the marked changes in polymorph count are features common to reactions occurring both in man and in the pig. A similar mechanism could be involved in the initiation of a reaction in both species, while species variation in the release of mediators, or the response to these mediators, could lead to some differences in the clinical signs produced. The pig has a greater basal concentration of plasma histamine than has man (Lorenz et al., 1971) and appears to metabolize endogenous histamine rapidly (unpublished observation). This may explain our failure to demonstrate increases in plasma histamine concentrations in every reaction. In addition, the release of histamine by compound 48/80 in the pig has been shown to produce a marked pressor response in this species (Lorenz et al., 1971). This pressor response may result from the secondary release of catecholamines.

A proportion of the reactions to i.v. agents which occur in man have been encountered on the first administration of an agent. These are believed to result, in some cases, from a direct pharmacological effect such as histamine release. In the majority of reactions occurring on the first administration of Althesin, complement C3 activation has been shown to be an important feature (Watkins, Udnoon et al., 1976). With one exception, the reactions in pigs occurred following prior exposure to a particular agent or solvent. The short interval required to induce sensitivity and the disappearance of this sensitivity after 3 weeks suggests that the reaction in the pig is unlikely to be a classical hypersensitivity response involving IgE. We have shown previously that, contrary to what one would expect with an anaphylactic response, animals which have responded to a second injection of Althesin have failed to respond fully to a further administration given 1 week after the second (Glen et al., 1978). Passive cutaneous anaphylaxis tests in pigs were negative and work is continuing to investigate the possible involvement of complement in the reaction.

A proportion of the reactions to Althesin in man occur when a second administration is given 1–4 weeks after a first. An analysis of the figures given in the report by Clark and others (1975) indicates that, excluding those patients with reactions of the delayed histaminoid type, 31 of the patients who reacted to Althesin had been exposed previously to a Cremophor-containing anaesthetic. In more than 50% of these patients the second administration had been given within 1 month of the first. Although IgE appears to be involved in some of the reactions to Althesin in man, it is thought unlikely that a conventional antibody response could be responsible for those reactions occurring within 1–4 weeks from a first exposure (Watkins, Allen and Milford Ward, 1978). These authors have suggested that a short-term "memory" phenomenon involving lymphocyte receptors and IgD may be responsible for these reactions.

If the reaction in the pig, where sensitivity is certainly of a short-term nature, can be thought to mimic this latter response in man, it seems reasonable to suggest that Cremophor and Micellophor are possibly responsible for at least a proportion of the reactions produced by Althesin and Epontol. The occurrence of reactions to alphaxalone and alphadolone in the absence of Cremophor suggests that the constituent steroids in Althesin may also contribute to some of the reactions seen with this agent.

We feel that the results obtained with Cremophor in the pig are sufficiently consistent to allow the model described here to be used for the evaluation of alternative surfactants for i.v. anaesthetics.

ACKNOWLEDGEMENTS

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MODELE ANIMAL RESERVE AUX ESSAIS DES REACTIONS ADVERSES AUX AGENTS ANESTHESIANTS ADMINISTRES PAR VOIE INTRAVEINEUSE ET A LEURS SOLVANTS

RESUME

Chez l'homme, le nombre des réactions adverses aux agents anesthésiants contenant du crémophor, tels que l'althésine et le propanidid (Epontol), a été signalé comme étant plus important que celles qui se produisent avec le thiopentone. La réaction du cobaye aux injections répétées d'une gamme d'agents anesthésiants et de leurs solvants, administrés par voie intraveineuse, a fait l'objet d'études afin d'essayer de découvrir le rôle éventuel du crémophor dans la production de ces réactions. Une seconde injection de crémophor EL ou de l'un des agents contenant du crémophor/micellophor, tels que l'althésine et le propanidid (Epontol), administrée 7 jours après la première a produit une haute fréquence de réactions adverses. Ce n'est qu'à une seule occasion, alors que l'on avait administré de l'alphaxalone et de l'alphadolone dans un mélange d'alcool et de propylène-glycol que l'on a constaté une réaction anormale lors de la première administration d'un agent quelconque. La seconde administration d'alphaxalone et d'alphadolone dans le même solvant a produit des réactions anormales chez deux cobayes sur quatre. Aucune réaction de ce genre n'avait été constatée lorsque le propanidid avait été administré dans de l'alcool et du propylène-glycol ou lorsque ce mélange solvant avait été administré seul. On n'a constaté aucune réaction anormale après l'administration répétée de thiopentone. Une augmentation marquée de la pression artérielle et une diminution marquée immédiate, mais transitoire, du nombre de leucocytes polymorphonucléaires en circulation ont été constatées uniformément chez les animaux ayant eu des réactions adverses. On n'a trouvé aucune réaction anormale lorsque l'intervalle entre les deux administrations d'althésine a été porté à 3 semaines.

EIN TIERMODELL FÜR DIE UNTERSUCHUNG NACHTEILIGER REAKTIONEN AUF INTRAVENÖSE NARKOSEMITTEL UND IHRE LÖSEMITTEL

ZUSAMMENFASSUNG

Den Berichten nach ist beim Menschen die Anzahl nachteiliger Reaktionen auf die Cremophor-enthaltenden Narkotika Althesin und Propanidid (Epantol) grosser, als die bei Thiopenton festgestellte. Die Reaktion des Kleinschweins auf wiederholte Injektion einer Reihe Narkotika und ihrer Losemittel wurde untersucht in einem Versuch, die mögliche Rolle von Cremophor beim Hervorrufen dieser Reaktionen festzustellen. Eine, 7 Tage nach der ersten eingegebene zweite Injektion von Cremophor El bzw. den Cremophor/Micellophor-enthaltenden Mitteln Althesin und Propanidid (Epantol) bewirkte eine grosse Anzahl nachteiliger Reaktionen. Nur bei einer Gelegenheit, bei der Alphaxalon und Alphadolon in einer Alkohol- und Propylenglykolmischung verabreicht wurden, wurde bei der ersten Verabreichung irgendeines Mittels eine ungewohnliche Reaktion beobachtet. Die zweite Verabreichung von Alphaxalon und alphadolon im selben Losemittel rief bei zwei von vier Schweinen ungewohnliche Reaktionen hervor. Keine solche Reaktionen wurden beobachtet, wenn Propanidid in Alkohol und Propylenglykol verabreicht wurde oder wenn diese Lösemittelmischung für sich allein verabreicht wurde. Nach wiederholter Verabreichung von Thiopenton wurden keine ungewöhnlichen Reaktionen beobachtet. Ein deutlicher Anstieg im arteriellen Blutdruck und ein unmittelbarer, aber vorübergehender deutlicher Abfall in der Anzahl an im Umlauf befindlichen polymorphkernigen Leukozyten wurden bei Tieren mit nachteiligen Reaktionen konsequent festgestellt. Wenn die Zeit zwischen zwei Verabreichungen von Althesin auf 3 Wochen verlängert wurde, wurden keine ungewohnlichen Reaktionen festgestellt.

UN MODELO ANIMAL PARA LA INVESTIGACION DE RESPUESTAS ADVERSAS A LOS AGENTES ANESTETICOS I.V. Y SUS SOLVENTES

SUMARIO

Se informó que en el hombre el número de respuestas adversas a los agentes anestéticos que contienen cremofor, Altesina y Propanidato (Epontol), es mayor del producido por la tiopentona. Se investigó la respuesta del minicerdo a inyecciones repetidas de una variedad de anestéticos y de sus solventes al tratar de cerciorarse sobre el posible papel del cremofor en la producción de dichas respuestas. Una segunda inyección de cremofor EL o de agentes que

contienen cremofor/micelofor, Altesina y Propanidato (Epontol), administrada 7 días después de la primera, produjo una alta frecuencia de respuestas adversas. En una sola oportunidad, cuando se administró alfaxalona y alfadolona en una mezcla de alcohol y de glicol de propileno, se registró una respuesta anormal en la primera administración de cualquier agente. La segunda administración de alfaxalona y de alfadolona en el mismo solvente provocó respuestas anormales en dos de los cuatro cerdos. No se registraron respuestas similares cuando se administró el propanidato en alcohol y glicol de propileno o cuando esta mezcla solvente se inyectó sola. Tampoco hubo respuestas anormales después de la administración repetida de tiopentona. Un aumento marcado de la tensión arterial y un descenso notorio inmediato aunque transitorio de las cantidades de leucocitos polimorfonucleares circulantes constituyeron resultados constantes en los animales que demostraban respuestas adversas. Cuando se extendió hasta 3 semanas el intervalo entre las dos administraciones de Altesina, no se registraron respuestas anormales.

Br. J. Anaesth. (1979), **51**, 829

EFFECTS OF METOPROLOL ON SYSTEMIC HAEMODYNAMICS, MYOCARDIAL PERFORMANCE AND THE CORONARY CIRCULATION DURING HALOTHANE ANAESTHESIA

G. BURT AND P. FOËX

SUMMARY

The effects of metoprolol 1 mg kg^{-1} i.v. on the systemic and coronary circulations and on myocardial performance were studied in nine open-chested dogs ventilated with halothane 0.8% in oxygen at normocarbia. In terms of the chronotropic effect, this dose of metoprolol produced a substantial shift to the right of the dose–response curve to isoprenaline: substantial reductions of arterial pressure (10%), cardiac output (21%), aortic blood acceleration (13%), left ventricular d*P*/d*t* max (13%) and left ventricular power (25%) were observed. Both preload, represented by left ventricular end diastolic pressure, and afterload, represented by systemic vascular resistance, increased. Left circumflex coronary blood flow and myocardial oxygen consumption decreased by approximately the same amount as peak ventricular power.

Metoprolol (CGP 2175: H 93/26) is an adrenergic beta-receptor antagonist. It has become more widely used clinically since the serious side-effects of practolol were reported (Brown et al., 1974; Marshall et al., 1977) and that drug withdrawn for chronic use in October 1975. A major difference between metoprolol and practolol is the lack of intrinsic sympathomimetic activity (i.s.a.) in the former. In the course of a study designed to investigate the role of beta-adrenergic mechanisms in the circulatory responses to varying arterial oxygen tension, metoprolol was used to block the cardiac beta receptors. The circulatory effects of the drug were marked.

METHODS

Nine healthy mongrel dogs (weight 12.5–25 kg) were studied. Premedication with morphine 0.4 mg kg^{-1} was given only when the animals responded poorly to handling (two dogs). Anaesthesia was induced with thiopentone 15 mg kg^{-1} i.v. and, after tracheal intubation, was maintained with 0.7–1% halothane in oxygen. Artificial ventilation at a tidal volume of 50 ml kg^{-1} and a rate of 12 b.p.m. was maintained with a Penlon–Oxford constant volume ventilator (Penlon Ltd, Abingdon). Arterial P_{CO_2} was maintained at about 5.5 kPa by adding carbon dioxide to the inspired gas mixture and monitoring end-tidal carbon dioxide concentration with an infra-red carbon dioxide analyser (Hartman Braun, URAS 4). A thermistor probe was inserted into the oesophagus and connected to a digital readout (Digitec 501 NSR 1K) with a feedback to an undertable heater so as to maintain body temperature within the range 36–38 °C. An i.v. infusion of physiological saline was given at a rate of 5 ml kg^{-1} h^{-1} using a Tekmar T92 infusion pump. E.c.g. monitoring was established using standard limb leads. A 20-cm Teflon catheter was inserted into the left common carotid artery and advanced until its tip lay in the ascending aorta: it was connected to a Statham P23 De pressure transducer. Through a left lateral thoracotomy with excision of the fifth rib, a cuffed electromagnetic flow transducer (SEM 230 series, SE Laboratories) was implanted around the ascending aorta and coupled to a sine wave electromagnetic flowmeter (type SEM 275, SE Laboratories). A Portex catheter (i.d. 1.2 mm) was inserted through the wall of the infundibulum of the right ventricle and directed through the pulmonary valve so that its tip lay in the main pulmonary artery. A similar catheter was inserted into the left atrium and both were connected to a Statham P23 De pressure transducer. A Portex catheter was introduced into the coronary sinus for blood sampling. A miniature strain gauge pressure transducer (Type P19 Konigsberg Instruments Inc., Pasadena, California) was inserted into the cavity of the left ventricle. The left circumflex coronary artery was exposed and a 2-mm SEM 230 flow transducer placed around it. This was connected to a type 275 electromagnetic flowmeter linked to the aortic flowmeter in a "master/slave" fashion to avoid

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interference. A pneumatic occluder was also placed around the left circumflex coronary artery, distal to the flow transducer, to allow determination of the zero flow signal.

After completion of surgery the chest was left open and an arterial blood sample was taken and analysed. The i.v. infusion was adjusted in relation to the blood loss and any metabolic acidosis was corrected with a bolus of 4.2% sodium bicarbonate. The experimental programme did not begin until at least 1 h had elapsed from the end of surgery.

The aortic flowmeter signal was integrated electronically to give beat-by-beat estimates of stroke volume (SV) and differentiated to give aortic blood acceleration (dQ/dt). The derived stroke volume was calibrated *in vivo* against simultaneous estimates of cardiac output and stroke volume obtained by the dye dilution technique using indocyanine green. The maximum rate of increase of left ventricular pressure (max LV dP/dt) was obtained by differentiating the left ventricular pressure signal. All these variables were recorded on an eight-channel inkjet recorder (Elema–Schonander EM81). A detailed account of the amplitude/frequency responses of the aortic flow transducer and of the left ventricular intracavitary pressure transducer has been given in a previous paper (Roberts et al., 1976), with details of the methods used for calibration of the signals.

Arterial, mixed venous and coronary sinus blood samples were analysed for Po_2, Pco_2 and pH using conventional electrode systems and amplifiers described by Hahn (1969, 1971). Corrections were applied for temperature and elapsed time according to Kelman and Nunn (1966) and a blood-gas difference of 1.04 was assumed for Po_2 (Prys-Roberts, 1968). Haemoglobin concentration was measured with a spectrophotometer (Bausch & Lamb Inc., Rochester, N.Y.).

Calculations

The data read from steady-state recordings were stored and the calculations performed on a Hewlett-Packard Calculator 9825A.

Systemic vascular resistance (SVR) was calculated as the ratio of mean systemic arterial pressure and cardiac output, neglecting mean right atrial pressure (McDonald, 1960; Gersh, Prys-Roberts and Baker, 1972) and expressed in kPa litre^{-1} s.

Max LV dP/dt was divided by the instantaneous developed pressure in the ventricle (IP) to give the index of myocardial contractility (max LV $(dP/dt)/\mathrm{IP}$) which has been described by Veragut and Krayenbühl (1965) and reassessed in this department by Gersh (1970) and Prys-Roberts and others (1972). Peak left ventricular power was calculated as the product of peak left ventricular pressure and peak aortic blood flow. Left ventricular stroke work was calculated as the product of mean arterial pressure and stroke volume and expressed in millijoules (mJ).

Left ventricular minute work was calculated from LVSW and heart rate. The product of heart rate and systolic arterial pressure was also calculated, as this has been suggested as a guide to myocardial oxygen consumption (Sarnoff et al., 1958). Oxygen saturation was calculated using the dissociation curve of Rossing and Cain (1966). In the calculation of oxygen content, an oxygen combining capacity of 1.34 ml oxygen per gram of haemoglobin was used (Hüfner, 1894; Foëx et al., 1970). Myocardial oxygen consumption was calculated as the product of the arterial to coronary sinus oxygen content difference and coronary blood flow and expressed in ml min^{-1}/100 g. The results were analysed for statistical significance using the paired *t* test.

Experimental programme

This study comprised part of another experiment and only the section of the programme relevant to the present paper is described below.

The dogs were ventilated with halothane 0.8 vol% in oxygen, with added carbon dioxide to maintain an end-expired carbon dioxide concentration of 5.2%. The inspired oxygen concentration was monitored continuously using a Servomex paramagnetic analyser and the halothane concentration using a Hook and Tucker ultraviolet analyser. A dose–response curve to isoprenaline was determined with the infusion rate doubled at each stage from an initial rate of 25 ng kg^{-1} min^{-1}.

Twenty minutes after completion of this stage, blood was sampled simultaneously from the aorta, pulmonary artery and coronary sinus. Subsequently, haemodynamic variables were recorded. A dose of metoprolol 1 mg kg^{-1} was injected slowly. This dose was chosen on the basis of a beta-2 potency approximately one-third that of propranolol (Ablad et al., 1975). Twenty minutes later the measurements were repeated. A second dose–response curve to isoprenaline was then obtained.

At the end of the experiment the coronary artery flow transducer was calibrated by infusing measured volumes of blood into the left circumflex coronary artery. The heart was removed and weighed.

RESULTS

The dose of metoprolol chosen produced an eightfold shift in the dose–response curve to isoprenaline (fig. 1). The effects of metoprolol on systemic haemodynamics are shown in table I. Heart rate decreased by 21%, as did cardiac output, there being no change in stroke volume. Despite an increase of 14% in systemic vascular resistance, systemic arterial pressure decreased by approximately 10%. Mean left ventricular end-diastolic pressure increased from 0.4 to 0.6 kPa. The changes in myocardial performance after metoprolol are shown in table II. The indices of myocardial contractility all showed significant reductions. Aortic blood acceleration and LV $\mathrm{d}P/\mathrm{d}t$ max both decreased by 13%. Reductions of similar magnitude were seen in peak left ventricular power (25%), left ventricular minute work (31%) and rate pressure product (23%). Metoprolol caused a 13% reduction in both LV $\mathrm{d}P/\mathrm{d}t$ max/IP and left ventricular stroke work. Left circumflex coronary flow was reduced by 25% and myocardial oxygen consumption decreased by 27%.

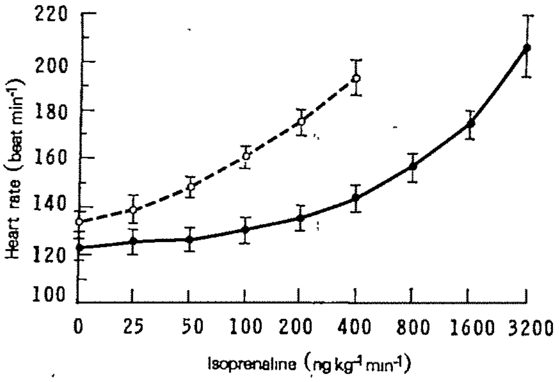

FIG. 1. The chronotropic response to isoprenaline infusion (cumulative doses) in nine dogs. ○—○ control; ●——● after metoprolol 1 mg kg^{-1}.

TABLE I. *Effects of metoprolol on the systemic circulation in nine dogs anaesthetized with halothane (mean ± SEM). Symbols for statistical significances for two-tailed Student's* t *tests, compared with control:* $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.005$

	Control	Beta blockade
Heart rate (beat min^{-1})	143 ± 10	114 ± 4**
Systolic arterial pressure (kPa)	13.2 ± 0.5	12 ± 0.4***
Diastolic arterial pressure (kPa)	10 ± 0.7	8.7 ± 0.5***
Stroke volume (ml)	14.1 ± 1.7	13.8 ± 1.7
Cardiac output (ml kg^{-1} min^{-1})	105 ± 8	83 ± 7***
Systemic vascular resistance (kPa $litre^{-1}$ s)	335 ± 40	384 ± 54*
Peak aortic flow (ml s^{-1})	162 ± 18	134 ± 16***
Left ventricular end-diastolic pressure (kPa)	0.4 ± 0.1	0.6 ± 0.1*

Table III shows that the arterial blood-gas values were similar before and after beta blockade. The only significant change seen in these data was a reduction in mixed venous oxygen tension after metoprolol. Coronary sinus oxygen tension was unchanged.

DISCUSSION

The effects of an adrenergic beta-receptor antagonist on the circulation depend not only on the properties and dose of the drug, but also on the pre-existing level of sympathetic activity.

TABLE II. *Effects of metoprolol on myocardial performance and coronary blood flow in nine dogs anaesthetized with halothane (mean ± SEM). Symbols for statistical significances for two-tailed Student's* t *tests, compared with control:* $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.005$

	Control	Beta blockade
$\mathrm{d}Q/\mathrm{d}t$ max (ml s^{-2})	4464 ± 409	3049 ± 308***
$\mathrm{d}P/\mathrm{d}t$ max (kPa s^{-1})	221 ± 12	153 ± 9***
$\mathrm{d}P/\mathrm{d}t$ max/IP (s^{-1})	33.4 ± 1.6	28.9 ± 1.8***
Peak LV power (W)	2.2 ± 0.3	1.6 ± 0.2***
LV stroke work (mJ)	156 ± 21	136 ± 18***
LV minute work (J)	22.3 ± 3.1	15.5 ± 2.1***
HR × SAP × 10^{-2}	19.1 ± 1.7	13.7 ± 0.8***
Left circumflex coronary flow (ml min^{-1} per 100 g)	14.3 ± 1.1	10.7 ± 0.8***
Myocardial oxygen consumption (ml min^{-1} per 100 g)	1.5 ± 0.1	1.1 ± 0.1***

TABLE III. *Blood-gas before and after metoprolol* 1 *mg* kg^{-1} *in nine dogs (mean ± SEM). Symbol for statistical significance for two-tailed Student's* t *test, compared with control:* $^{***}P < 0.005$

	Control	Beta blockade
$P\mathrm{a}_{O_2}$ (kPa)	66.2 ± 2.5	69.8 ± 1.4
$P\mathrm{a}_{CO_2}$ (kPa)	5.8 ± 0.2	5.8 ± 0.1
pHa (unit)	7.35 ± 0.01	7.35 ± 0.01
$P\bar{v}_{O_2}$ (kPa)	7.4 ± 0.2	6.8 ± 0.2***
$P\bar{v}_{CO_2}$ (kPa)	7.1 ± 0.2	7.3 ± 0.2
pH$\bar{v}$ (unit)	7.30 ± 0.01	7.30 ± 0.01
$P\mathrm{cs}_{O_2}$ (kPa)	4.3 ± 0.2	4.4 ± 0.2
$P\mathrm{cs}_{CO_2}$ (kPa)	7.9 ± 0.3	8.0 ± 0.2
pHcs (unit)	7.30 ± 0.01	7.29 ± 0.01

In the resting unanaesthetized dog, Pitt, Green and Sugishita (1970) found no significant changes in heart rate, mean arterial pressure, cardiac output, coronary blood flow and late diastolic coronary vascular resistance after propranolol 1 mg kg^{-1}. This suggested that beta-adrenergic activity is minimal in the resting, intact animal.

Under anaesthesia the level of sympathetic activity will depend upon a number of complex factors, including the properties of the anaesthetic agents used, the depth of anaesthesia, the amount of surgical trauma and the arterial carbon dioxide tension. Such factors were not always controlled adequately in many of the earlier experiments on beta-adrenergic blockade, and this may have contributed to the inconsistent results.

This criticism does not apply to the study of Merin and Tonnesen (1969) who examined the effects of propranolol 0.25 mg kg^{-1} in eight dogs under light halothane anaesthesia. Cardiac output and left ventricular stroke work decreased whilst mean arterial pressure, left ventricular end-diastolic pressure and systemic vascular resistance increased with no changes in heart rate, left ventricular dP/dt max, myocardial blood flow and myocardial oxygen consumption.

When using practolol 1.25 mg kg^{-1} in a similar preparation, Merin (1972) found increases in heart rate (14%), mean arterial pressure (27%), systemic vascular resistance (31%), left ventricular stroke work (11%), left ventricular dP/dt max (11%), myocardial blood flow (51%) and myocardial oxygen extraction (28%). There was no change in cardiac output or left ventricular end-diastolic pressure.

These findings contrast markedly with our results. A major difference between the two drugs is that intrinsic sympathomimetic activity is a feature of the action of practolol but not of metoprolol (Ablad et al., 1975). Other factors contribute to the different responses to the two drugs. The doses chosen may not be strictly comparable, since Roberts (1974) found that even a larger dose of practolol (2 mg kg^{-1}) produced only a six-fold shift in the dose-response curve to isoprenaline in a preparaton similar to ours. Also the level of sympathetic activity before blockade is likely to be greater in our open-chest preparation than in the dogs studied by Merin when the catheters were sited under fluoroscopic control.

The higher degree of sympathetic activity may also explain why a greater reduction of cardiac output was observed after metoprolol than after administration of practolol or propranolol in previous studies (Prys-Roberts et al., 1976).

The 27% decrease in myocardial oxygen consumption seen after metoprolol was of the same order of magnitude as the reduction in indices of myocardial performance, as would be expected from the work of Braunwald (1971). An attempt was made to correlate myocardial oxygen consumption with left ventricular stroke work, left ventricular minute work and peak left ventricular power, but no correlation was found. Figure 2 demonstrates this finding in this series of experiments, including values observed when the inspired oxygen fraction was varied (30% and 15%). The rate-pressure product proved to be a better guide to myocardial oxygen consumption and the relationship did not change after metoprolol (fig. 3).

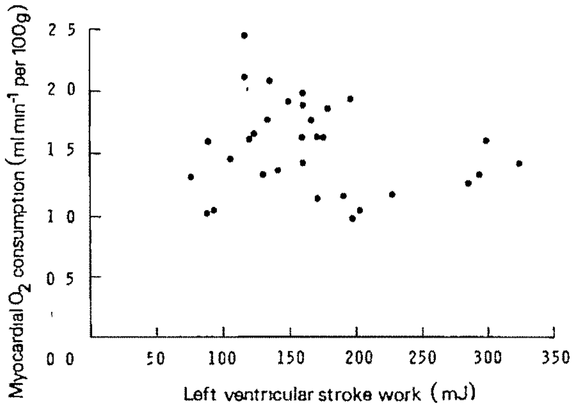

FIG. 2. Diagrammatic representation of the left ventricular stroke work and myocardial oxygen consumption in nine dogs. There is no relationship between the two variables ($r = 0.02$; P not significant).

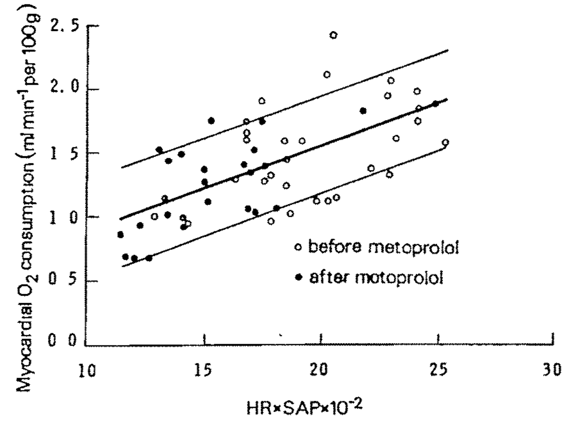

FIG. 3. Relationship between rate-pressure product and myocardial oxygen consumption in nine dogs before (○) and after (●) beta-adrenergic blockade. The 95% confidence intervals are shown ($r = 0.63$; $P < 0.05$; 8 degrees of freedom).

The question remains as to which is the safest adrenergic beta-receptor antagonist for use during halothane anaesthesia. Merin concluded that practolol is more suitable than propranolol, since cardiac output and arterial pressure did not decrease. However, the increase in myocardial oxygen consumption induced by practolol is potentially dangerous if the increase in myocardial blood flow is compromised by coronary vascular disease. Metoprolol reduced the oxygen requirements of the myocardium, but a reduction in cardiac output of 21% in a circulatory system already depressed by halothane may be unsatisfactory. We feel that some intrinsic sympathomimetic activity is a desirable feature of the action of a selective adrenergic beta-1-receptor antagonist so that cardiac output may be maintained; however, the drug should not cause a significant increase in myocardial oxygen demand.

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EFFETS DU METOPROLOL SUR L'HEMODYNAMIQUE SYSTEMIQUE, LES PERFORMANCES MYOCARDIALES ET LA CIRCULATION CORONAIRE PENDANT L'ANESTHESIE A L'HALOTHANE

RESUME

On a étudié sur neuf chiens, ayant la poitrine ouverte et ventilée à l'halothane (0,8%) dans l'oxygène à normocarbie, les effets du métoprolol administré par voie intraveineuse à raison de 1 mg kg^{-1} sur la circulation systémique

et sur la circulation coronaire de même que sur les performances myocardiales. En termes d'effets chronotropiques, cette dose de métoprolol a produit un déplacement marqué vers la droite de la courbe dose–réaction à l'isoprénaline et on a observé: des réductions substantielles de la pression artérielle (10%) du débit cardiaque (21%) de l'accélération du sang aortique (13%), de la $\mathrm{d}P/\mathrm{d}t$ maximale ventriculaire gauche (13%) et de la puissance ventriculaire gauche (25%). La précharge, représentée par la pression diastolique d'extrémité ventriculaire gauche, tout comme l'après-charge, représentée par la résistance vasculaire systémique, ont diminué. Le débit sanguin coronaire circonflexe gauche et la consommation d'oxygène myocardial ont diminué d'à peu prês la même quantité que la puissance ventriculaire de pointe.

DIE WIRKUNGEN VON METOPROLOL AUF DIE SYSTEMISCHE HÄMODYNAMIK, DIE HERZMUSKELLEISTUNG UND DEN KORONAREN KREISLAUF WÄHREND EINER HALOTHANNARKOSE

ZUSAMMENFASSUNG

Es wurden die Wirkungen von 1 mg/kg intravenös eingegebenem Metoprolol auf die systemischen und koronaren Kreisläufe und die Herzmuskelleistung in neun, mit (0,8%) Halothan in Sauerstoff bei normalem Kohlensäuregehalt im Blut ventilierten Hunden mit offenem Brustkorb untersucht. Hinsichtlich der chronotropen Wirkung verursachte diese Metoprololdosis eine wesentliche Verschiebung nach rechts der Dosenreaktionskurve auf Isoprenalin: es wurden wesentliche Ruckgange im arteriellen Druck (10%), Herzminutenvolum (21%), der aortischen Blutbeschleunigung (13%), dem linksventrikulären $\mathrm{d}P/\mathrm{d}t$ max (13%) und der linksventrikulären Kraft (25%) beobachtet. Sowohl die durch den linksventrikulären und diastolischen Blutdruck angezeigte Vorbelastung als auch die durch den systemischen Gefasswiderstand angezeigte Nachbelastung stiegen an. Der links umgebogene koronare Blutstrom und der Sauerstoffverbrauch des Herzmuskels fielen um ungefahr die gleiche Menge, wie die maximale ventrikuläre Kraft.

EFECTOS EJERCIDOS POR METOPROLOL SOBRE LA HEMODINAMICA SISTEMICA, RENDIMIENTO MIOCARDIAL Y LA CIRCULACION CORONARIA DURANTE LA ANESTESIA DE HALOTANO

SUMARIO

Se estudiaron los efectos ejercidos por metoprolol 1 mg kg^{-1} intravenoso sobre las circulaciones sistémica y coronaria y sobre el rendimiento miocardial en nueve perros con tórax abierto ventilados con halotano 0,8% en oxígeno a normocarbia. En cuanto al efecto cronotrópico, esta dosis produjo un desplazamiento considerable a la derecha de la curva de reacción a la dosis de isoprenalina: se observó una considerable reducción en la presión arterial (10%), capacidad cardíaca (21%), aceleración aórtica de la sangre (13%), $\mathrm{d}P/\mathrm{d}t$ max del ventrículo izquierdo (13%) y fuerza del ventrículo izquierdo (25%). Aumentó tanto la precarga, representada por la presión ventricular izquierda y la diastólica final, como la postcarga, representada por la resistencia vascular sistémica. La circulación sanguínea coronaria circumfleja y el consumo de oxígeno miocardíaco disminuyeron aproximadamente en la misma cantidad que la potencia ventricular máxima.

Br. J. Anaesth. (1979), **51**, 835

INHIBITION OF NEURONAL AND EXTRANEURONAL UPTAKE OF NORADRENALINE BY KETAMINE IN THE ISOLATED PERFUSED RAT HEART

P. J. SALT, P. K. BARNES AND F. J. BESWICK

SUMMARY

The effect of ketamine on the uptake of ^{3}H-noradrenaline in the isolated perfused rat heart was studied. A dose-dependent inhibition of uptake by both neuronal and extraneuronal processes was found. These effects may account for the positive chronotropic and pressor effects of the drug.

The administration of ketamine is associated with an increase in arterial pressure and tachycardia (Corssen and Domino, 1966; Virtue et al., 1967). For these reasons it has been recommended as the agent of choice in patients with hypovolaemic shock (Dillon, 1971) and for the aged and seriously ill in order to avoid cardiovascular collapse on induction of anaesthesia (Horatz and Speh, 1973). The cardiovascular effects of ketamine may contraindicate its use in patients with hypertension (Langrehr and Neuhaus, 1973; Kaukinen, 1978).

Although evidence has been produced for a vagolytic action (Traber, Wilson and Priano, 1971), the cardiovascular effects of ketamine appear to result mainly from its interaction with the sympathetic nervous system. Ketamine stimulates the central sympathetic nervous system directly (Slogoff and Allen, 1974; Wong and Jenkins, 1974) and indirectly by desensitization of baroreceptors (Dowdy and Kaya, 1968). Ketamine has been shown to inhibit the uptake of noradrenaline (NA) into the isolated rat heart (Miletich et al., 1973), the isolated rabbit heart (Hill et al., 1978) and into rabbit aorta and pulmonary artery strips (Nedergaard, 1973).

It has been postulated by these workers and others (Montell et al., 1973) that ketamine blocks neuronal re-uptake of noradrenaline (Uptake$_1$) (Iversen, 1963). This study was designed to examine inhibition of Uptake$_1$ by ketamine in greater detail, and to look for possible inhibition of extraneuronal uptake of noradrenaline (Uptake$_2$) (Iversen, 1965) in the isolated perfused rat heart.

METHODS

Male albino Wistar rats weighing 150–250 g were killed by cervical dislocation and the hearts removed and perfused by the Langendorff technique as described previously (Iversen, 1963). The perfusion medium was a Krebs-Henseleit solution containing glucose 1 g litre^{-1} to which was added EDTA disodium salt at a concentration of 10 mg litre^{-1} and ascorbic acid 20 mg litre^{-1} to reduce auto-oxidation of noradrenaline (NA). The Krebs solution was gassed with 5% carbon dioxide in oxygen and maintained at 37 °C. After perfusion for 1 min with amine-free solution, the hearts were perfused with Krebs solution containing (±)-^{3}H-noradrenaline (^{3}H-NA) (The Radiochemical Centre, Amersham; 13.0 Ci mmol^{-1}) diluted with non-radioactive (±)-NA to a final concentration of 10 ng ml^{-1} and 50 nCi ml^{-1} for Uptake$_1$ experiments and 5 μg ml^{-1} and 125 nCi ml^{-1} for Uptake$_2$ experiments (Salt, 1972). Ketamine was dissolved directly in this Krebs solution containing NA immediately before each experiment. For Uptake$_1$ screening, perfusion was continued with NA for 10 min, and in the case of Uptake$_2$ for 4 min. The hearts were removed, blotted free of perfusion medium and homogenized in 1% EDTA 2 ml; 10 ml of acid ethanol was added and the samples centrifuged at 3000 rev min^{-1} for 10 min. The radioactivity in 1-ml aliquots of the supernatant was measured in a Packard Tri-Carb liquid scintillation spectrometer after adding Biofluor 15 ml (New England Nuclear) as scintillator. The tissue content of labelled NA plus metabolites was calculated after correcting for the presence of ^{3}H-NA in the extracellular space and, in the case of Uptake$_2$, for the uptake of ^{3}H-NA into sympathetic

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nerve terminals (Iversen and Salt, 1970). Six hearts were perfused at each concentration of ketamine. A log-probit plot of the results for Uptake$_1$ and Uptake$_2$ was made, and the line of best fit was obtained by the method of least squares. From these plots the concentration of ketamine producing 50% inhibition of each uptake process (IC$_{50}$) was calculated.

RESULTS

Ketamine produced a concentration-dependent inhibition of both Uptake$_1$ and Uptake$_2$ (figs 1, 2). The IC$_{50}$ values for the two processes, determined from the plots, were almost identical (table I). However, the slopes of the dose-response curves differed markedly, that for Uptake$_1$ inhibition being much steeper than that for Uptake$_2$ inhibition (1.45 compared with 0.95 probit/log units), suggesting that the type of inhibition may not be the same at these two anatomically different sites.

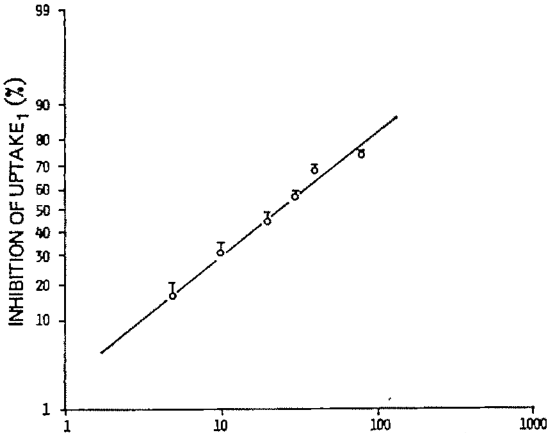

FIG. 1. Inhibition of Uptake$_1$ by ketamine. Percentage inhibition of ^{3}H-NA Uptake$_1$ (probability scale) is plotted against log concentration of ketamine: line fitted by the method of least squares analysis. Each point is the mean value for six hearts. SEM indicated by vertical lines. Uptake of ^{3}H-NA in control hearts was 136 ± 5.2 ng g^{-1} (mean ± SEM for six hearts).

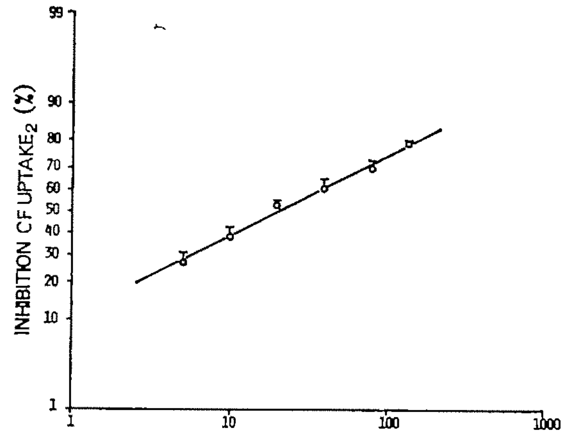

FIG. 2. Inhibition of Uptake$_2$ by ketamine. Percentage inhibition of ^{3}H-NA Uptake$_2$ (probability scale) is plotted against log concentration of ketamine: line fitted by the method of least squares analysis. Each point is the mean value for six hearts. SEM indicated by vertical lines. Uptake of ^{3}H-NA in control hearts was 3.70 ± 0.25 μg g^{-1} (mean ± SEM for 12 hearts).

TABLE I. *IC$_{50}$ values for Uptake$_1$ and Uptake$_2$ and regression coefficients. IC$_{50}$ values were determined as the concentration of ketamine causing 50% inhibition in figures 1 and 2. The regression coefficient represents the gradient of the line of best fit, determined by the method of least squares analysis for each graph*

	Uptake$_1$	Uptake$_2$
IC$_{50}$ (μg ml^{-1})	23.4	19.9
Regression coefficient (probit/log units)	1.45	0.95

DISCUSSION

The action of released NA is terminated by uptake into neuronal and extraneuronal tissue (fig. 3). Uptake into sympathetic nerve terminals occurs at low concentrations of NA, and has been termed "Uptake$_1$" by Iversen (1963). At greater concentrations of NA a more rapid accumulation of catecholamine occurs. This results from uptake into cardiac muscle itself, a process designated "Uptake$_2$" (Iversen, 1965).

This study shows that ketamine acts upon both Uptake$_1$ and Uptake$_2$. Our results therefore confirm those of previous workers with respect to Uptake$_1$ inhibition by ketamine (Miletich et al., 1973; Nedergaard, 1973). Nedergaard also found that ketamine potentiated the effects of exogenous NA and of sympathetic nerve stimulation, as would be expected if this mechanism for the inactivation of NA were blocked by the drug (Trendelenburg, 1959). However, in our experiments with rat hearts, Uptake$_2$ was also affected significantly by ketamine, and this has not been demonstrated previously. Hill and others (1978) investigated the effects of ketamine on the isolated perfused rat heart. Their results suggested that ketamine may act as an Uptake$_1$ blocker, although they could find no potentiation of the inotropic effects

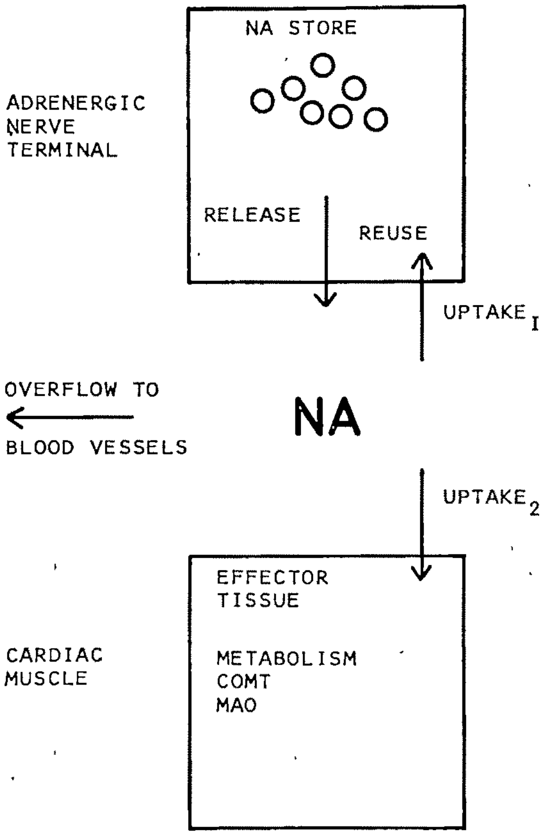

FIG. 3. Fate of noradrenaline (NA) at the adrenergic nerve terminal.

of isoprenaline, which is the substrate of choice for Uptake$_2$ and is not transported into Uptake$_1$ sites (Callingham and Burgen, 1966). The discrepancy between the findings of Hill and others (1978) and the present work may result from the different species examined, although in the experiments of Hill a high concentration of isoprenaline (100 ng ml^{-1}) was used; presumably it would have been difficult to demonstrate potentiation of the already maximal response to isoprenaline.

In the present investigation it was found that the dose–response curves for inhibition of Uptake$_1$ and Uptake$_2$ overlapped to such an extent that both processes were affected almost identically at any given concentration of ketamine. This drug is therefore unique amongst those agents which block uptake of NA into tissues because most uptake inhibitors are selective for just one process (Salt, 1972). Those relatively few compounds which are known to block both the noradrenergic uptake mechanisms show a preference for one or the other process, for example phenoxybenzamine (Uptake$_1$ IC$_{50}$ = 0.2 μmol litre^{-1}; Uptake$_2$ IC$_{50}$ = 2.5 μmol litre^{-1}) (Iversen, Salt and Wilson, 1972). Uptake inhibitors which block only one of the processes potentiate the effects of NA and cause a greater proportion of the sympathetic transmitter to be taken up by the other unaffected side (Eisenfeld, Landsberg and Axelrod, 1967; Iversen, Salt and Wilson, 1972). When both uptake mechanisms are inhibited simultaneously, as with ketamine, the potentiation of the response to NA might be expected to be amplified to an even greater extent. Blockade of both uptake mechanisms may also be associated with overflow of the released sympathetic transmitter into the systemic circulation (Brown and Gillespie, 1957) and increased plasma noradrenaline concentrations have been reported in patients following injection of ketamine (Zsigmond, 1972).

The cardiovascular effects of ketamine have been well documented. Its chronotropic and pressor effects in rats (Chang, Chan and Ganendran, 1969), dogs (McCarthy et al., 1965; Dowdy and Kaya, 1968) and man (Domino, Chodoff and Corssen, 1965; Corssen and Domino, 1966; Morgan et al., 1971) may be explained by inhibition of both neuronal and extraneuronal uptake processes for NA by ketamine.

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INHIBITION DE LA FIXATION DE LA NORADRENALINE PAR LA KETAMINE DANS LES NEURONES ET EN-DEHORS DES NEURONES DU CŒUR ISOLE ET IRRIGUE DU RAT

RESUME

On a fait une étude sur l'effet qu'a la kétamine sur la fixation de la noradrénaline H^3 sur le cœur isolé et irrigué du rat. On a constaté une inhibition de la fixation, en fonction de la dose administrée, par les procédés se rapportant aux neurones et en-dehors des neurones. Ces effets pourraient justifier les effets chronotropiques positifs et pressifs du médicament.

HEMMUNG DER NORADRENALINAUFNAHME IN UND AUSSERHALB DER NERVENZELLEN DURCH KETAMIN IM ISOLIERTEN DURCHSTRÖMTEN RATTENHERZ

ZUSAMMENFASSUNG

Es wurde die Wirkung von Ketamin auf die Aufnahme von 3H-Noradrenalin im isolierten durchströmten Rattenherz untersucht. Es wurde eine dosis-bezogene Hemmung der Aufnahme durch Prozesse in den Nervenzellen wie auch ausserhalb derselben festgestellt. Es ist moglich, dass die chronotropen und blutdruckerhohenden Wirkungen des Arzneimittels durch diese Wirkungen erklart werden.

INHIBICION DE LA ABSORCION NEURONAL Y EXTRANEURONAL DE NORADRENALINA POR KETAMINA EN EL CORAZON AISLADO Y PERFUCIONADO DE LA RATA

SUMARIO

Se estudió el efecto ejercido por la ketamina sobre la absorción de noradrenalina ^{3}H en el corazón aislado y perfusionado de la rata. Se descubrió una inhibición dependiente de la dosis, afectando los procesos tanto neuronal como extraneuronal. Estos efectos podrían explicar los efectos cronotrópico e hipertensor positivos de la droga.

Br. J. Anaesth. (1979), **51**, 839

METABOLISM OF SYNTHANE: COMPARISON WITH *IN VIVO* AND *IN VITRO* DEFLUORINATION OF OTHER HALOGENATED HYDROCARBON ANAESTHETICS

R. I. MAZZE, W. J. BEPPU AND B. A. HITT

SUMMARY

Aerobic defluorination of the inhalation anaesthetic agent, synthane, was compared with that of methoxyflurane, enflurane and halothane and with two other anaesthetics, isoflurane and sevoflurane. *In vitro*, in microsomes prepared from phenobarbitone-induced and control livers, synthane and halothane were not defluorinated. The relative order of defluorination of the other anaesthetics was, methoxyflurane > sevoflurane > enflurane > isoflurane. *In vivo*, following 4 h of 1.2% (MAC) synthane anaesthesia, urinary inorganic fluoride excretion was increased by only a trivial amount and only in phenobarbitone-treated rats; polyuria was not observed. Synthane is the least metabolized of the fluorinated ether anaesthetics; its administration will not result in inorganic fluoride nephropathy. An index of nephrotoxic potential for fluorinated anaesthetic agents was formulated utilizing *in vitro* fluoride production data and oil : gas partition coefficients.

In vivo biotransformation of an inhalation anaesthetic agent was first demonstrated by Barrett and Johnston (1939) who recovered trichloroacetic acid from the urine of dogs anaesthetized with trichloroethylene. Metabolism of other inhalation anaesthetics was not reported until 1964 when Van Dyke, Chenoweth and Van Poznak, using radioactive labelled compounds demonstrated the *in vivo* metabolism of chloroform, diethyl ether, halothane and methoxyflurane. The first *in vitro* studies reporting metabolism of halogenated hydrocarbons were by Heppel and Porterfield (1948), who demonstrated enzymatic dehalogenation of a series of brominated and chlorinated methanes and ethanes by a halidase in rat liver. Van Dyke and Chenoweth (1965) applied these techniques to investigate biotransformation of fluorinated inhalation anaesthetic agents. Since then, all halogenated anaesthetics have been found to be biotransformed by animals and human beings. The present study examines the *in vitro* and *in vivo* defluorination of synthane (BAX 3224; difluormethyl 1,2,2,3,3-pentafluoropropyl ether), a non-flammable investigational inhalation anaesthetic agent. The properties of synthane are: empirical formula, $C_4H_3F_7O$; boiling point (101.3 kPa), 75 °C; liquid density (23 °C), 1.55 g ml^{-1}; vapour pressure (20 °C), 12 kPa; water : gas partition coefficient (37 °C), 1.6; blood : gas partition coefficient (37 °C), 2.5; oil : gas partition coefficient (corn oil, 37 °C), 95; and MAC (canine), 1.2% (Travenol Laboratories, Chicago, Illinois: *Summary of Information on BAX* 3224, *a New General Anesthetic Agent*, April 21, 1972).

METHODS

In vitro studies

Fourteen adult male Fischer 344 rats, weighing 338 ± 9 g (mean ± SEM), bedded on ground corn cob for 30 days were assigned randomly to two groups. One group drank plain tap water *ad libitum*. The other drank tap water which contained sodium phenobarbitone 1 mg ml^{-1} for 7 days before sacrifice to induce the mixed-function oxidase system (Marshall and McLean, 1969). Animals were fasted overnight, then sacrificed by decapitation. Livers were excised and immediately placed in ice-cold Tris–HCl buffer 0.05 mol $litre^{-1}$, pH 7.4, and microsomes prepared in standard fashion (Mazze, Hitt and Cousins, 1974). The microsomal pellet was suspended in buffer, so that the final protein concentration was 5 mg ml^{-1}, and then assayed immediately.

Optimal *in vitro* reaction conditions for defluorination of the various anaesthetic substrates were determined by varying protein concentration, amount of cofactors and reaction time. These conditions were then employed for the definitive experiments as noted below. Assays were carried out in 25-ml sealed reaction flasks which contained: microsomal protein

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5 mg, NADP 25 μmol, glucose 6-phosphate 10 μmol and glucose 6-phosphate dehydrogenase 1 unit in a total volume of 5 ml. Reaction flasks were gassed with oxygen for 2 min at 1 litre min^{-1} and then sealed. Reactions were started by adding one of the anaesthetics in liquid form to give a concentration of 1 mmol litre^{-1}; this corresponds to an *in vivo* blood anaesthetic partial pressure approximately equal to the partial pressure at MAC. Aqueous phase concentrations were verified by gas chromatography during the last 5 min of the reaction. Two reactiion flasks and two control flasks were prepared from each preparation for each assay. The first control flask contained anaesthetic but no microsomal protein and the second contained microsomal protein but no anaesthetic. All flasks were incubated for 30 min at 37 °C with constant agitation; under these conditions defluorination was linear with time. Reactions were stopped by unsealing the flasks and heating to 60 °C. The mixtures were evaporated to dryness and resuspended in 1 ml of sodium acetate buffer 2.5 mol litre^{-1}, pH 4.8. Inorganic fluoride activity was determined with an Orion ion specific electrode (Fry and Taves, 1970). Inorganic fluoride reference standards were prepared by adding known amounts of sodium fluoride to reaction flasks containing all constituents of the reaction mixture except the anaesthetic agent. Rates of inorganic fluoride production were determined by subtracting the rate of fluoride production in the control flasks from the rate in the flasks with complete reaction mixtures.

In vivo studies

Ten adult male Fischer 344 rats, weighing 354 ± 10 g, bedded on ground corn cob for 30 days were divided randomly into two treatment groups of equal size and placed in individual metabolic cages. After a 3-day adaptation period three control 24-h urine collections were obtained, following which one group of rats drank tap water *ad libitum*; the other group drank tap water containing sodium phenobarbitone 1 mg ml^{-1} for 7 days. Both groups of rats were placed in a Plexiglass chamber of volume 100 litre where synthane was administered for 4 h. In order to conserve the drug a closed system was employed. Soda-lime was placed on the floor of the anaesthetic chamber to a depth of 12.7 mm and plastic wire mesh was laid on top of it. After the rats were in the chamber, 10 ml of liquid synthane was sprayed on a gauze sponge and vaporized within the chamber. Ambient synthane concentration was measured by gas chromatography and 2–5-ml increments of drug were vaporized approximately every 15 min to maintain a concentration of 1.2% as determined by gas chromatography. Oxygen was added to the chamber, intermittently, to maintain an atmospheric concentration of 50%. After anaesthesia, rats received 100% oxygen until awake, then were returned to their individual metabolic cages where 24-h urine collections were obtained for the next 3 days. Urinary output and inorganic fluoride excretion were determined for each rat for each day.

Statistical analyses

Mean values for each treatment group were determined. Comparisons were made using paired and unpaired *t* tests. $P<0.05$ was considered statistically significant.

RESULTS

In vitro

Synthane and halothane were not defluorinated to a degree measurable by our methods in either control or phenobarbitone-induced hepatic microsomal preparations (table I). In control preparations (C), methoxyflurane and sevoflurane defluorination rates

TABLE I. *Results of* in vitro *experiments.* n = 7, *all groups. SYN = synthane; HAL = halothane; ISO = isoflurane; ENF = enflurane; SEVO = sevoflurane; MOF = methoxyflurane.* $P<0.05$: * v. *ENF, SEVO and MOF*; † v. *MOF*; ‡ v. *SEVO and MOF*; § v. *control, same agent*; ¶ v. *all other groups*

	F^{-} (nmol 30 min^{-1} per mg protein)					
	SYN	HAL	ISO	ENF	SEVO	MOF
Control (C)	<0.1	<0.1	0.51*	1.31†	1.82	2.00
mean ± SEM			±0.09	±0.23	±0.30	±0.11
Induced (I)	<0.1	<0.1	1.51‡§	1.63‡§	3.22†§	18.89§
mean ± SEM			±0.25	±0.15	±0.46	±2.40
I/C	—	—	3.60¶	1.35¶	1.90¶	9.75¶
mean ± SEM			±0.80	±0.15	±0.25	±1.50

were approximately the same and were greater than enflurane and isoflurane rates, respectively. For drugs with measurable rates of defluorination, phenobarbitone treatment (I) increased the rate of defluorination in all cases, but to different degrees, as shown by the values I/C (table I). The relative order of defluorination, however, remained the same.

In vivo

Rats were rapidly and smoothly anaesthetized following vaporization of synthane in the anaesthetic chamber. They recovered from anaesthesia quickly and without difficulty. After anaesthesia polyuria was not observed in either group (table II). Before anaesthesia, urinary inorganic fluoride excretion was 2.7 ± 0.1 μmol day^{-1} in both control and phenobarbitone-treated rats (table II); after anaesthesia, urinary inorganic fluoride excretion increased significantly ($P < 0.05$), but only in phenobarbitone-treated rats on day 1 after anaesthesia. The increase in inorganic fluoride excretion (fig. 1), however, was very small compared with that observed in previous studies from our laboratory with methoxyflurane, isoflurane, enflurane and sevoflurane (Mazze, Cousins and Kosek, 1972; Cousins et al., 1973; Barr et al., 1974; Cook et al., 1975a). The order of defluorination in the present study compared with the above experiments, in all of which non-induced rats received approximately the same anaesthetic exposure, 4–5 MAC hours, was: methoxyflurane > sevoflurane = enflurane > isoflurane > synthane = halothane = control.

Figure 2 compares urinary inorganic fluoride excretion data from the present study with data from other experiments in which phenobarbitone-treated and control rats received identical exposures to the same agent, although anaesthetic dosage varied from agent to agent (Barr et al., 1974; Mazze, Hitt and Cousins, 1974; Cook et al., 1975b). Synthane was defluorinated by induced rats only; isoflurane and enflurane were defluorinated by control and phenobarbitone-treated rats to approximately the same extent; phenobarbitone treatment increased urinary inorganic fluoride excretion compared with control when sevoflurane or methoxyflurane was administered subsequently.

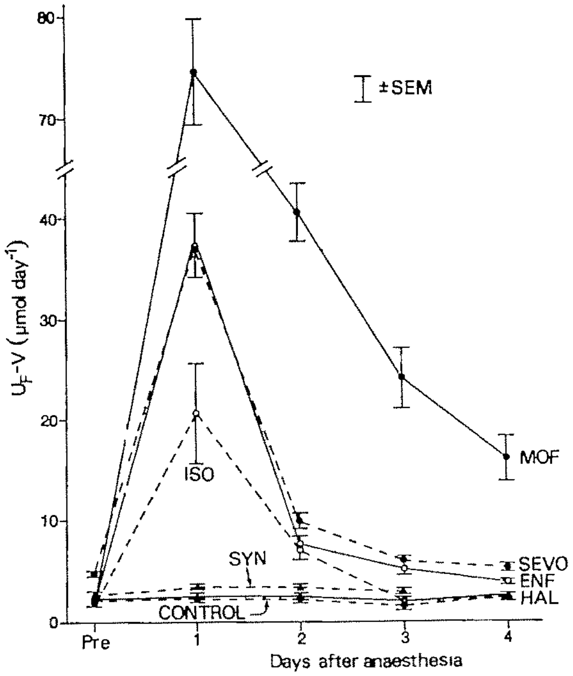

FIG. 1. Urinary inorganic fluoride excretion (U_F-V) following administration of fluorinated hydrocarbon anaesthetic agents to non-induced rats. Anaesthetic exposure in each case was 4–5 MAC hours. The relative ease of defluorination was MOF > SEVO = ENF > ISO > SYN = HAL = control. Abbreviations: SYN = synthane: ISO = isoflurane; ENF = enflurane; SEVO = sevoflurane; MOF = methoxyflurane; Pre = before anaesthesia.

DISCUSSION

The results of the present study indicate that, under aerobic conditions, synthane is not significantly defluorinated *in vitro* and is only minimally defluorinated

TABLE II. *Twenty-four hour urinary output and inorganic fluoride excretion, before and after synthane anaesthesia; mean ± SEM.* * $P < 0.05$ v. *before anaesthesia (Pre)*

	Urinary output (ml day^{-1})				Urinary F^- excretion (μmol day^{-1})			
	Pre	Day 1	Day 2	Day 3	Pre	Day 1	Day 2	Day 3
Control	7.8	7.1	7.9	8.0	2.7	3.5	3.4	3.0
($n = 5$)	±0.5	±0.6	±0.6	±0.7	±0.1	±0.5	±0.4	±0.3
Induced	6.9	7.3	7.2	6.7	2.7	4.6*	4.1	3.5
($n = 5$)	±0.6	±0.7	±0.5	±0.5	±0.1	±0.2	±0.2	±0.5

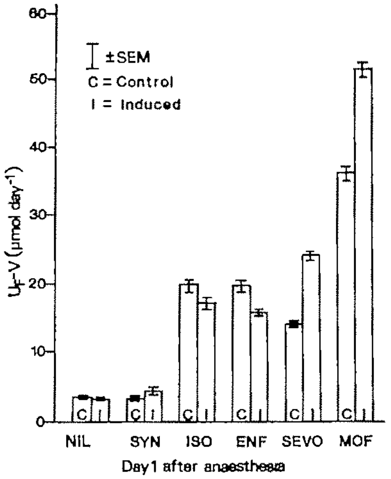

FIG. 2. Urinary inorganic fluoride excretion (U_F_V) day 1 after anaesthesia, in which rats were either treated with phenobarbitone (I) or untreated (C). All rats received identical exposures to the same anaesthetic agent, although anaesthetic exposure from agent to agent may have varied. Prior phenobarbitone treatment increased (U_F_V) only when sevoflurane or methoxyflurane was administered. SYN = synthane; ISO = isoflurane; ENF = enflurane; SEVO = sevoflurane; MOF = methoxyflurane; NIL = no anaesthesia.

in vivo by Fischer 344 rats. These results are consistent with the findings of Sawyer and others (1975) who administered synthane to *Macaca speciosa* monkeys. Fluorine is the only halogen atom found in the synthane molecule, so that oxidation at any point will lead to the formation of unstable intermediates and ultimately to the liberation of free inorganic fluoride ions. Although a similar absence of inorganic fluoride was noted in experiments with halothane, the same conclusion concerning its biotransformation would not be correct. Oxidative metabolism of halothane to the organic fluoride metabolites, trifluoroacetic acid and trifluoroethanolamide, without formation of inorganic fluoride, has been reported (Cohen et al., 1975).

The present study compares *in vivo* and *in vitro* synthane defluorination with defluorination of several other inhalation anaesthetic agents both clinically available and under investigation. *In vivo* studies with Fischer 344 rats are of value in predicting the nephrotoxic potential of fluorinated inhalation agents in patients. In both man and rats, exposure to methoxyflurane leads to dose-related increases in serum inorganic fluoride with concentrations as great as 250 μmmol litre⁻¹; this is associated with vasopressin-resistant, polyuric nephropathy (Mazze, Cousins and Kosek, 1972; Cousins and Mazze, 1973). In both species, prolonged enflurane exposure results in moderate increases of serum inorganic fluoride with concentrations of 35–50 μmol litre⁻¹ occasionally noted; this is associated with a sub-clinical concentrating defect (Barr et al., 1974; Mazze, Calverley and Smith, 1977). Isoflurane and halothane administration do not cause inorganic fluoride concentrations in excess of 2–6 μmol litre⁻¹; this is not associated with impaired urinary concentrating ability (Cousins et al., 1973; Mazze, Cousins and Barr, 1974).

While *in vivo* studies with Fischer 344 rats may be the most unequivocal approach apart from human investigations for examining anaesthetic-induced nephropathy, compared with *in vitro* studies they are costly and time consuming. Since the inhalation anaesthetics are nephrotoxic only as a consequence of their defluorination, a more convenient method of screening for nephrotoxic potential might be simply to measure *in vitro* inorganic fluoride formation. However, duration of the increase in serum inorganic fluoride bears on the development of nephrotoxicity. Assuming that exposure to the fluorinated anaesthetic agents is the same, the area under the serum inorganic

TABLE III. *Nephrotoxic potential of fluorinated anaesthetic agents. MOF = methoxyflurane; DOC = dioxychlorane; ENF = enflurane; SEVO = sevoflurane; ISO = isoflurane; HAL = halothane; SYN = synthane*

Agent	F^- (nmol 30 min⁻¹ per mg protein)	×	λ (oil : gas)	=	Defluorination index	Nephrotoxic potential
MOF	2.00		930		1860	1.00
DOC	1.41		275		387	0.23
ENF	1.31		99		129	0.07
SEVO	1.82		56		101	0.05
ISO	0.51		94		48	0.03
HAL	0		230		0	0.00
SYN	0		95		0	0.00

fluoride or urinary inorganic fluoride excretion curves is related to the biological stability of the anaesthetic agent and the solubility of the drug in body tissues, particularly fat. Thus we have formulated a defluorination index which is the product of *in vitro* inorganic fluoride formation and the oil : gas partition coefficient of the anaesthetic agent (table III). The index for methoxyflurane, 1860, has been assigned a nephrotoxic potential of one. Other drugs have been given proportional values based on their defluorination index. The derived values appear to correlate well with the demonstrated nephrotoxicity of the fluorinated inhalation agents tested to date.

Such an index also may have predictive value for new agents. We recently tested dioxychlorane ($C_3H_2Cl_2F_2O_2$), an experimental inhalation anaesthetic agent of dioxalane ring structure (Denson et al., 1976), in our hepatic microsomal preparation. Inorganic fluoride production was 1.41 nmol per 30 min per milligram of protein. The oil : gas partition coefficient of dioxychlorane is 275 (table III). These data yielded a defluorination index of 387 and a nephrotoxic potential of 0.23, a value considerably greater than that calculated for enflurane, sevoflurane or isoflurane. Because of this, dioxychlorane was not synthesized commercially and *in vivo* confirmation in our laboratory of *in vitro* results was not possible.

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METABOLISME DU SYNTHANE: COMPARAISON DE LA DEFLUORATION *IN VIVO* ET *IN VITRO* AVEC LES AUTRES AGENTS ANESTHESIANTS A BASE D'HYDROCARBURES HALOGENES

RESUME

La défluoration aérobie du synthane, agent anesthésiant par inhalation, a été comparée à celle du méthoxyflurane, de l'enflurane et de l'halothane de même qu'à deux autres anesthésiques: l'isoflurane et la sévoflurane. *In vitro*, dans des microsomes préparés à partir de foies traités et contrôlés par le phénobarbitone, le synthane et l'halothane n'ont pas été défluorés. L'ordre relatif de la défluoration des autres agents anesthésiants a été méthoxyflurane > sévoflurane > enflurane > isoflurane. *In vivo*, après 4 h d'anesthésie au synthane à 1,2% (MAC), l'excrétion urinaire de fluorure inorganique n'a augmenté que d'une quantité négligeable et seulement dans le cas des rats traités au phénobarbitone; on n'a observé aucune polyurie. Le synthane est le moins métabolisé des agents anesthésiants fluorés à base d'éther; son administration ne

produira pas de néphropathie de fluorure inorganique. Il a été préparé un index du potentiel néphrotoxique des agents anesthésiants fluorés à l'aide des données de production du fluorure obtenues *in vitro* et des coefficients de séparation de l'huile et du gaz.

SYNTHANSTOFFWECHSEL: VERGLEICH MIT *IN VIVO* UND *IN VITRO* DURCHGEFÜHRTER DEFLUORINIERUNG ANDERER HALOGENIERTER KOHLENWASSERSTOFFNARKOTIKA

ZUSAMMENFASSUNG

Die aerobische Defluorinierung des Inhalationsnarkotikums Synthan wurde mit der von Methoxyfluran, Enfluran und Halothan und mit zwei anderen Narkotika, nàmlich Isofluran und Sevofluran, verglichen. Synthan und Halothan wurden *in vitro*, in aus mit Luminal behandelten und Kontrollebern praparierten Mikrosomen, nicht defluoriniert. Die Defluorinierung der anderen Narkotika betrug, in relativer Grossenordnung: Methoxyfluran > Sevofluran > Enfluran > Isofluran. *In vivo* war nach 4 Stunden Synthannarkose (1,2%—hochstzulässige Konzentration) die Urinausscheidung von anorganischem Fluorid nur unbedeutend hoher, und nur in mit Luminal behandelten Ratten; es wurde keine Polyurie beobachtet. Synthan ist das am wenigsten umgesetzte der fluorinierten Äthernarkotika; seine Verabreichung hat kein, von anorganischem Fluorid herruhrendes Nierenleiden zur Folge. Es wurde ein Index des nierenschädigenden Potentials fur fluorinierte Narkotika formuliert under Verwendung der *in vitro* erhaltenen Fluoriderzeugungsdaten und der Öl : Gas-Teilungskoeffizienten.

METABOLISMO DE SINTANO: COMPARACION CON LA DEFLUORACION *IN VIVO* Y *IN VITRO* DE OTROS ANESTESICOS DE HIDROCARBURO HALOGENADO

SUMARIO

Se comparó la defluoración aerobia del agente anestésico inhalado sintano con la de metoxiflurano, enflurano y halotano y con dos otros anestésicos, isoflurano y sevoflurano. *In vitro*, en microsomas preparados con hígados inducidos por fenobarbitona y otros de control, tanto el sintano como el halotano no fueron defluorados. El orden relativo de defluoración de los demás anestésicos fue metoxiflurano > sevoflurano > enflurano > isoflurano. *In vivo*, tras 4 h de anestesia con 1,2% de sintano (MAC), la excreción de fluoruro inorgánico urinario aumentó solamente en una cantidad trivial y únicamente en ratas tratadas con fenobarbitona; no se observó poliuria. El sintano es el menos metabolizado de los anestésicos de éter fluorado; su administración no causará nefropatía de fluoruro inorgánico. Se formuló un índice del potencial nefrotóxico de agentes anestésicos fluorados, utilizando datos de producción de fluoruro *in vitro* y coeficientes de repartición de aceite:gas.

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AMBIENT AIR CONTAMINATION IN A DENTAL OUTPATIENT THEATRE

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SUMMARY

The extent of air contamination by halothane in an operating session was correlated with the number of patients, the total usage of halothane, refilling a vaporizer and the number of hyperventilating patients per session. Trichloroethylene content of theatre air correlated only with total usage and refilling a vaporizer. A very strong personal association ($P \ll 0.001$) was found between the anaesthetist and the extent of air contamination with halothane. The association was weaker ($0.05 < P < 0.1$) for trichloroethylene. The median ambient air contamination with halothane in the vicinity of the faces of anaesthetists and dental surgeons was between six and nine times greater than the median air contamination at the fixed sampling sites ($P \ll 0.005$).

Although contamination of operating theatre atmospheres by anaesthetic agents occurs, controversy has arisen over the health risks to people working in such an environment. If the risks are difficult to quantify, the extent of air contamination can be measured accurately, although the problems involved are considerable. It is important to have reliable, precise and accurate data for establishment of current normal contamination patterns in theatres of various designs and with various work patterns, in order to determine the nature and extent of the risks of exposure and to test the effectiveness of contamination control systems. For toxicological studies to be effective, reliable data on exposure patterns are needed.

In a previous communication (Robinson et al., 1976), the importance of accuracy and precision was stressed, and associated problems of sampling, measurement and calibrations, and statistical treatment of results, were discussed and some solutions were proposed. The present study applies to an outpatient dental theatre in a dental hospital. Vapours of anaesthetic agents are discharged into operating theatre air, not only from patients' expired gases, but also from filling and draining of vaporizers, whether or not spillage occurs; they are also released through leakage from ill-fitting joints (Berner, 1973). Account was taken of such factors in this study.

METHODS

The atmospheric concentrations of halogenated anaesthetic agents were measured by an automatic sampler unit and a gas chromatograph incorporating a variable frequency pulsed electron capture detector (Robinson et al., 1976). Air samples were drawn automatically through various long, narrow nylon catheters (3.2 mm o.d., 1.2 mm i.d., 15–18 m long). The catheters terminated at various fixed sites and on the persons of the anaesthetist and of the dentist. These catheters were attached to clothing, with the sampling site near to the neck. This system was calibrated using primary absolute standards prepared in a diffusion dilution apparatus (Barratt, Jones and Thompson, 1975). Measurements of air movements in the operating theatre were made using a purpose-built hot wire anemometer (Hutton and Thompson, 1975) in order to assess the distribution.

The survey of air quality was made in an outpatient dental theatre at the Birmingham Dental Hospital over a period of 3 months. The theatre was 4.9 m square and 3.2 m high with one wall of singly-glazed windows along its whole length at a height of 0.95 m above the floor. The dental chair was placed almost

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centrally beside the suspended unit of gas supply lines. There were two doorways in the room, and a plenum ventilation system, with two entry points and one exhaust point. The engineers' specification for the theatre ventilation system was for 20 air changes per hour in the room. This specification refers to the volume of air delivered by the inlet fan. Figure 1 represents the general arrangement of this theatre and shows the location of the sampling points. Eleven consultant or senior registrar anaesthetists worked in the theatre and used a variety of anaesthetic procedures. In addition, dental students were sometimes present for instruction in either anaesthesia or extraction techniques. The cases dealt with were mostly emergency extractions. The anaesthetic machine used in the theatre was a B.O.C. Walton 5, delivering nitrous oxide and oxygen through a nasal mask continuously during induction and on demand during maintenance of anaesthesia. Halothane and trichloroethylene vaporizers (Drawover Fluotec and Tritec) were fitted in series on the Walton 5 machine, although some anaesthetists removed one vaporizer. As most operations were rather short, the anaesthetist was asked to record the maximum concentration used during an operation. Table I lists the factors recorded by the anaesthetist on a record sheet supplied by us.

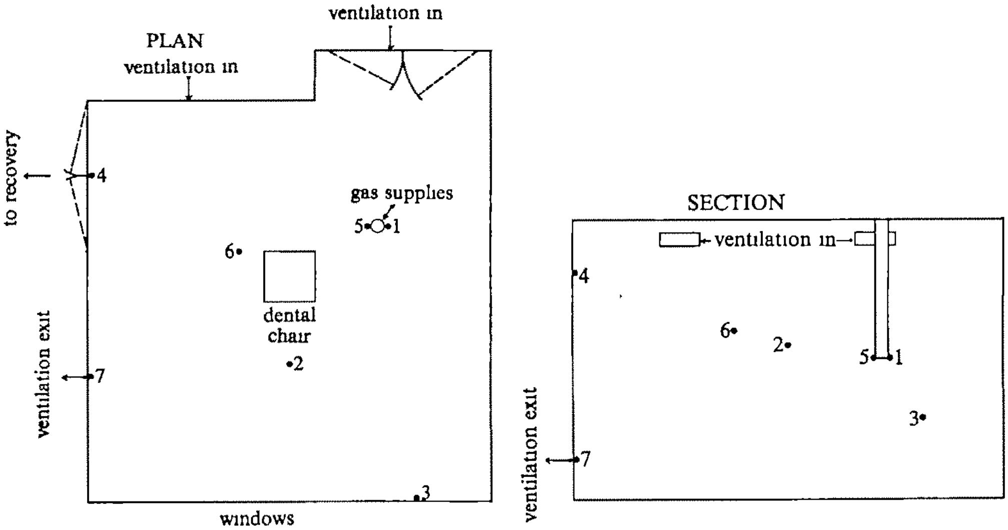

FIG. 1. The arrangement of the outpatient theatre at the Birmingham Dental Hospital showing the location of the seven fixed sampling sites.

Samples of air were taken during a total of 48 sessions, 26 mornings and 22 afternoons. Throughout each session samples were injected into the gas chromatograph at regular 5-min intervals. In some sessions all samples were drawn from the anaesthetist's line (6½ sessions, 202 samples), or all from the dentist's line (three sessions, 108 samples), in others all samples were drawn from the fixed sampling sites, either:

(a) all seven sites in sequence (so that each site was sampled every 35 min) (28 sessions, 812 samples), or

(b) sites 1, 2, 5 and 6 (each site was sampled every 20 min) (10½ sessions, 384 samples).

TABLE I. *Factors noted on record sheet used by anaesthetists*

Anaesthetist
Date
Time (intervals of 5 min marked on sheet)
Vaporizer on Walton 5 (Fluotec, Tritec, Both)
Vaporizer setting (% halothane (0.5–3) in 0.5% steps, % trilene (0.25–1.5) in 0.25% steps)
Induction (i.v., continuous flow, intermittent (i.e. demand) flow)
Unusual events (window open, door open, empty or fill vaporizer, etc.)

The statistical methods used for comparing the concentration measurements at the fixed sampling sites, and for the comparisons of concentration measurements for personal monitoring with the overall fixed site sample population, are described in Appendix A. The methods used were non-parametric because the sample distributions were approximately exponential, rather than Gaussian in shape. Thus conclusions drawn from a parametric statistical analysis would have been invalid.

The relationship between the extent of contamination in a given operating session and the various factors influencing the contamination were established by simple correlation coefficient calculations described in Appendix B, as well as by Kruskal–Wallis analysis (Appendix A).

The sum of all the observed concentrations at a site in any one session was taken as an estimate of the total contamination at that site for that session. The factors likely to affect this total are listed in table II.

TABLE II. *Some factors influencing operating theatre air contamination*

Sampling location
Theatre ventilation system
Number of patients
Vaporizer refill
Vaporizer setting
Anaesthetist—method of anaesthesia
Presence of students giving anaesthetic
Hyperventilation during induction
Vaporizer on anaesthetic machine

Some factors may vary from session to session, but will remain constant within a session, for example the anaesthetist. However, other factors may vary within a session but cannot easily be related to particular measurements of concentration, for a variety of reasons. There can be a delay between the recorded event and its influence at a sampling site; also the recording of the various factors by the anaesthetists is inherently imprecise if only because of the low priority given to it in their activities. At each fixed sampling site, the air was sampled only intermittently with either a 35- or a 20-min interval between such samples. Therefore the magnitude of each of the factors which varied during a session was expressed as the sessional sum (of vaporizer settings) or the sessional number (of administrations, of vaporizer refillings, etc.). The dependence of the sums of observed concentrations on the sums of the various factors was then examined as described in Appendix B.

Blood halothane concentrations were measured before and after certain sessions for a small number of theatre personnel, merely as an exploratory exercise. The groups examined were (i) anaesthetists, (ii) theatre nurses, (iii) dental students giving anaesthetics, (iv) dental students undertaking extractions. Blood samples (2 ml each) were taken at the beginning of a session to determine "blank" values and at the end of an operating session to determine uptake of halothane during the session. Each sample (1 ml) was extracted using n-hexane 2 ml. Aliquots from the n-hexane extracts (1 µl) were injected into the gas chromatograph used for the analysis of halothane in air. All experimental conditions were the same as in the air contamination analysis.

RESULTS AND DISCUSSION

Fixed site and personal sampling

The sample population distribution of halothane concentrations for (a) all fixed sites, (b) personal monitoring of anaesthetists and (c) personal monitoring of dental surgeons is illustrated in figure 2.

Table III lists the arithmetic means and the medians; table IV lists the percentages of observations above particular arbitrarily chosen concentrations (100, 150 and 200 μg litre^{-1}) for each fixed site and table V lists similar data for the pooled observations

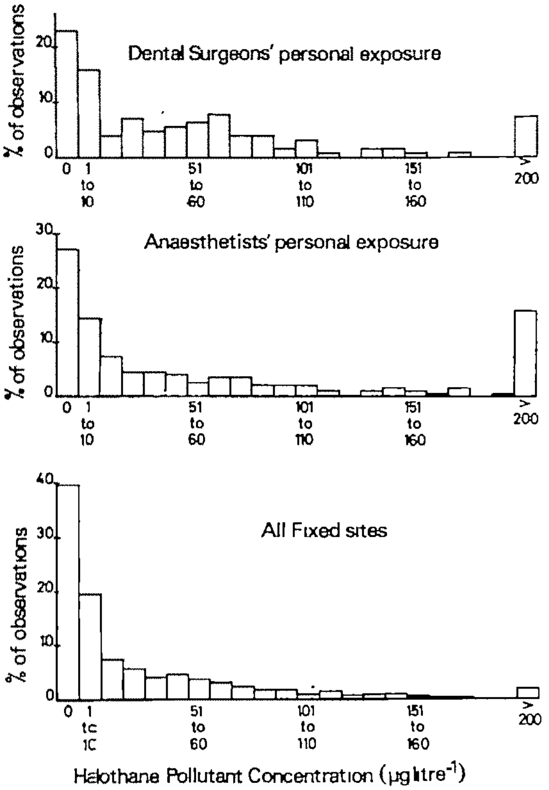

FIG. 2. Sampling population distributions of halothane concentrations in air for dental surgeons' personal exposure, anaesthetists' personal exposure and the pooled observations from all seven fixed sites.

TABLE III. *Arithmetic mean and median concentrations of halothane in air at the fixed sampling sites in the dental theatre*

Sample site no.	Sampling method	No. of observations	Arithmetic mean concn (μg litre^{-1})	Median concn (μg litre^{-1})
1	A‡	123	34.3	4.4
	B§	103	36.4	*
	Both†	226	35.3	3.85
2	A‡	122	31.1	3.3
	B§	103	30.2	*
	Both†	225	30.7	3.3
3	A‡	118	14.5	2.2
4	A‡	117	22.9	2.2
5	A‡	105	35.0	6.6
	B§	83	36.7	*
	Both†	188	35.8	5.7
6	A‡	113	39.3	5.5
	B§	95	29.8	*
	Both†	208	34.8	4.4
7	A‡	114	25.4	3.3
All fixed sites	Both†	1196	29.8	3.3

* Not calculated; †both indicates that observations made using each sampling method, A or B, were pooled; ‡each of all seven sites sampled every 35 min; §each of sites 1, 2, 5 and 6 sampled every 20 min.

TABLE IV. *Some cumulative distribution data for measurements of halothane concentrations in air at the fixed sites*

Sample site no.	No. of observations	% Observations of halothane concn in air (μg litre^{-1}) greater than 100	150	200
1	226	10.1	4.8	3.1
2	225	7.1	3.6	2.7
3	118	0.8	0	0
4	117	6.4	1.7	1.7
5	188	8.3	3.7	1.6
6	208	9.1	5.3	2.9
7	114	2.7	0.9	0
Pooled observations	1196	7.2	3.0	1.7

TABLE V. *Arithmetic mean and median concentrations and cumulative distributions for halothane in air for personal monitoring of anaesthetists and dental surgeons compared with pooled fixed site measurements. *Mean calculated from data which included observations where the gas chromatograph electron capture detector was saturated* (>5760 μg *litre*$^{-1}$)

	Anaesthetists	Dental surgeons	All fixed sites
Arithmetic mean concn (μg litre^{-1})	>284.5*	65.5	29.8
Median concentration (μg litre^{-1})	22	30	3.3
% Observations greater than 100μg litre^{-1}	24.9	15.9	7.2
150 μg litre^{-1}	20.4	8.7	3.0
200 μg litre^{-1}	16.9	7.1	1.7
No. of observations	202	108	1196

made at the fixed sites and for the personal sampling of anaesthetists and dental surgeons.

The fixed site arithmetic mean halothane concentrations ranged from 14.5 μg litre^{-1} (site 3) to 35.8 μg litre^{-1} (site 6), whereas the medians ranged from 2.2 μg litre^{-1} (sites 3 and 4) to 6.6 μg litre^{-1} (site 5). The median is a more useful, meaningful and representative measure of the location of the distribution when the latter is non-Gaussian. Kruskal–Wallis analysis (Kruskal and Wallis, 1952, 1953) of the seven fixed-site sample populations (Appendix A) shows that there is at least one pair of sites the medians of which differ significantly using the populations from both sampling methods combined (A: sites 1 to 7 consecutively; B: sites 1, 2, 5 and 6) with $P \ll 0.001$ and for sampling method A alone with P between 0.10 and 0.05. Multiple comparisons using Dunn's method (Dunn, 1964) (Appendix A) show that site 3 median is significantly smaller than site 5 median ($P = 0.005$ sample method A alone; $P = 0.10$ sample methods A and B together), and is also significantly smaller than the site 6 median ($P = 0.20$). No other significant difference between sites was noted.

There is some evidence (Thompson et al., 1977) that halothane 150 μg litre^{-1} may be equal to or greater than a threshold value for this drug, in that significant e.e.g. changes have been observed at this concentration in the atmosphere. The medians for the personal exposures of the anaesthetists and dental surgeons are significantly greater than the median for the pooled fixed site data ($P \ll 0.005$ for the one-sided version of the Kolmogorov–Smirnov two-sample test). From these tables it may also be noted that the anaesthetists' and dental surgeons' median personal exposures are between six and nine times greater than the median of the fixed site observations, whereas the arithmetic means are greater by between two and 10 times. It is not immediately obvious from table V that the percentage of observations greater than the specified halothane concentrations do not differ significantly for the anaesthetists and dental surgeons, but no significant difference was found between the personal exposures of these two groups (Kolmogorov–Smirnov two-sample test, two-sided version).

If it is assumed that the theatre ventilation is adequate to remove any air contamination between sessions or between individual operations, then it might be reasonable to suppose that atmospheric concentrations of halothane or trichloroethylene would remain small (possibly less than the set limit of detection of the analytical equipment), until either a patient is anaesthetized or the vaporizer is filled. Under such circumstances the atmospheric concentrations will increase and decrease quite rapidly, as illustrated in figure 3, for the anaesthetist's breathing zone.

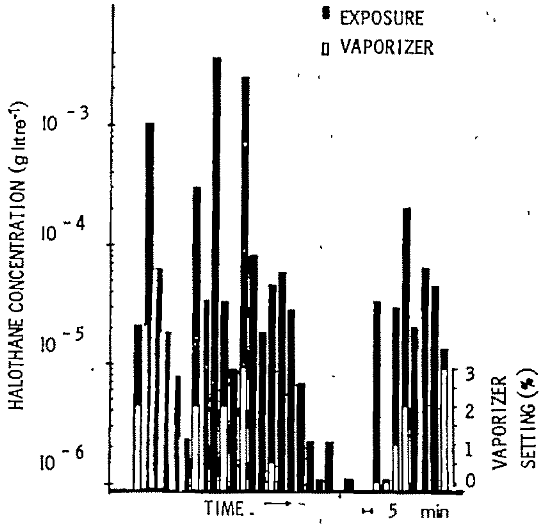

FIG. 3. The exposure of an anaesthetist to halothane during part of an operating session, illustrating the increase and decrease of the halothane concentration (contamination) in the air. Samples were taken at 5-min intervals from a sampling position on the front of the anaesthetist close to his neck. The white bars indicate the maximum vaporizer setting for each case, including those where the maximum was zero.

Effect of theatre activity

Table VI is a comprehensive table of correlation coefficients (r) and their associated probability values (P) showing the interrelationships between the various factors and their influence on theatre air contamination. The number of cases dealt with per session correlates well with the session total of halothane vaporizer settings, the number of halothane vaporizer refills and the session totals of halothane contamination and its natural logarithm. No such strong correlations are noted for the corresponding trichloroethylene variables; this anaesthetic agent was used much less frequently. As one would expect, there is a strong correlation between the sessional total of vaporizer settings and air contamination both for halothane and trichloroethylene. Vaporizer refills per session correlate only with the natural logarithm of the sessional air contamination, but not with the sessional total itself. This may be related to the fact that the sessional totals of air contamination have a skewed distribution, whereas the natural logarithms of these totals are more normally distributed. The natural logarithm of the sessional totals for halothane in air correlate well with the number of hyperventilating patients, as might be expected from the greater volumes of halothane-containing expired gases in such cases.

The influence of the anaesthetist upon the extent of air contamination was tested by a Kruskal–Wallis analysis (Kruskal and Wallis, 1952, 1953) (see Appendix A) of the sessional totals of halothane and of trichloroethylene in air for each anaesthetist. The anaesthetist had a strong influence on air contamination with halothane ($P \ll 0.001$), but only a weak influence on air contamination with trichloroethylene ($0.05 < P < 0.1$).

One factor shown in table I to be influencing the extent of contamination is the vaporizer on the machine, and this may seem a strange factor to consider. We have previously reported (Robinson, Thompson and Barratt, 1977) that a vaporizer can deliver volatile anaesthetic agents into the circuit even when turned off and the anaesthetic machine can deliver volatile anaesthetic agents, even when a vaporizer is not fitted. In the present study, trichloroethylene concentrations in the atmosphere of up to 12.5 μg litre^{-1} were found even when the drug was not part of the anaesthetic and the vaporizer was turned off. Trichloroethylene concentrations up to 2.2 μg litre^{-1} were measured when the vaporizer was not even on the anaesthetic machine. Such contamination of the atmosphere can arise from contamination of the anaesthetic machine, from contamination of the vaporizers in series or from contaminated hoses. Whilst this might be of considerable importance when dealing with a susceptible patient, it is only of minor significance as a contributor to pollution by the anaesthetic. The contamination of theatre air arising from vaporizer leakage or other sources is illustrated in figure 4. It is noteworthy that, in the sixth patient

TABLE VI. *Correlation coefficients showing interdependence of various factors influencing air contamination. CASES = number of cases per session; VAPH = sessional total of halothane vaporizer settings; VAPT = sessional total of trilene vaporizer settings; REFH = sessional total of halothane vaporizer refills; REFT = sessional total of trilene vaporizer refills; TOTH = sessional total of halothane concentration; TOTT = sessional total of trilene concentrations; NHYPERV = sessional total of hyperventilating patients; NOH and NOT = number of observations of halothane and trilene respectively. The correlation coefficients for the sessional duration of windows open, and doors open are not included, because all coefficients had probability values associated with them* > 0.2, *except for the sessional window open duration correlated with sessional total of trilene vaporizer refills* (r = 0.361, P = 0.0112) *and sessional total of trilene concentrations* (r = 0.320, P = 0.025). *There is no obvious reason for these latter two correlations*

		CASES	VAPH	VAPT	REFH	REFT	TOTH	TOTT	logTOTH	logTOTT	NHYPERV	NOH	NOT
CASES	*r*	1.0000											
	P	0.0000											
VAPH	*r*	0.743	1.0000										
	P	0.0001	0.0000										
VAPT	*r*	−0.102	−0.063	1.0000									
	P	0.501	0.674	0.0000									
REFH	*r*	0.271	0.275	−0.195	1.0000								
	P	0.059	0.056	0.180	0.0000								
REFT	*r*	−0.063	−0.061	0.116	0.378	1.0000							
	P	0.673	0.683	0.561	0.008	0.0000							
TOTH	*r*	0.267	0.338	−0.127	0.0314	−0.111	1.0000						
	P	0.064	0.0178	0.607	0.826	0.542	0.0000						
TOTT	*r*	−0.003	0.044	0.684	0.054	0.101	0.052	1.0000					
	P	0.984	0.766	0.0001	0.715	0.503	0.725	0.0000					
logTOTH	*r*	0.597	0.624	−0.288	0.278	−0.074	0.736	−0.043	1.0000				
	P	0.0001	0.0001	0.045	0.052	0.620	0.0001	0.768	0.0000				
logTOTT	*r*	−0.0299	0.062	0.725	0.070	0.335	−0.171	0.736	−0.268	1.0000			
	P	0.834	0.680	0.0001	0.641	0.0188	0.245	0.0001	0.063	0.0000			
NHYPERV	*r*	0.231	0.393	−0.074	0.570	0.333	0.155	0.199	0.350	0.201	1.0000		
	P	0.111	0.006	0.623	0.0001	0.0196	0.295	0.172	0.014	0.168	0.0000		
NOH	*r*	0.248	0.196	0.204	0.042	0.145	0.051	0.070	0.221	0.170	−0.151	1.0000	
	P	0.085	0.179	0.161	0.772	0.675	0.732	0.643	0.127	0.247	0.307	0.0000	
NOT	*r*	0.116	0.115	0.107	−0.054	0.054	0.031	−0.041	0.219	−0.020	−0.244	0.814	1.0000
	P	0.562	0.558	0.524	0.718	0.715	0.830	0.779	0.131	0.887	0.091	0.0001	0.0000

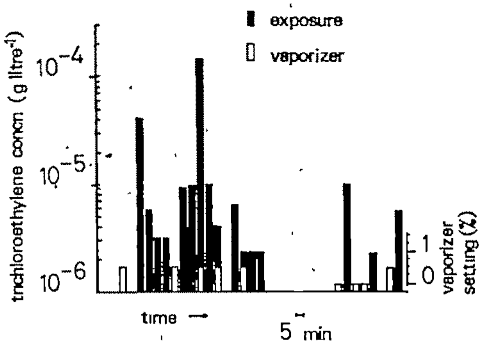

FIG. 4. The exposure of an anaesthetist to trichloroethylene during part of an operating session, illustrating the contamination of theatre as in figure 3 and also showing the contamination resulting from leakage of trichloroethylene from the vaporizer or other circuit components when this agent was not in use. Sampling conditions as for figure 3. The white bars indicate the maximum vaporizer setting for each case including those where the maximum was zero.

of the session, anaesthesia was induced with a barbiturate administered i.v., followed by maintenance with nitrous oxide in oxygen alone, but even so, in this case atmospheric concentrations of trichloroethylene increased quite considerably.

Theatre air movement and its effects

There are five main contributing factors which determine the overall air movement pattern in this theatre:

(1) a steady component provided by the plenum ventilation unit;
(2) a random fluctuation caused by the movement of doors, hatches and people;
(3) draughts from ill-fitting windows;
(4) when a large surface area of singly-glazed windows is present, and the external air temperature is low, there is a steady current of air provided by natural convection;
(5) other sources of natural convection; people standing or sitting in the theatre, x-ray viewers and theatre lights.

A schematic diagram illustrating the interaction of factors listed under 1, 3, 4 and 5 on the general pattern of air movement is shown in figure 5. The random fluctuations introduced under factor (2) will produce a variety of effects. Opening doors and hatches reduce the ability of the plenum ventilation system to maintain a stable pressurization of the theatre. Thus air movement patterns established during pressurization will be disturbed, so that air from the plenum entries will move along paths of low resistance to open doorways and hatches. Movements of people will generate air currents in the form of a wake with speeds of up to about 300 mm s^{-1}. Such wakes will only contribute significantly to air movement in areas of otherwise low speed air movements and when there are fairly frequent comings and goings.

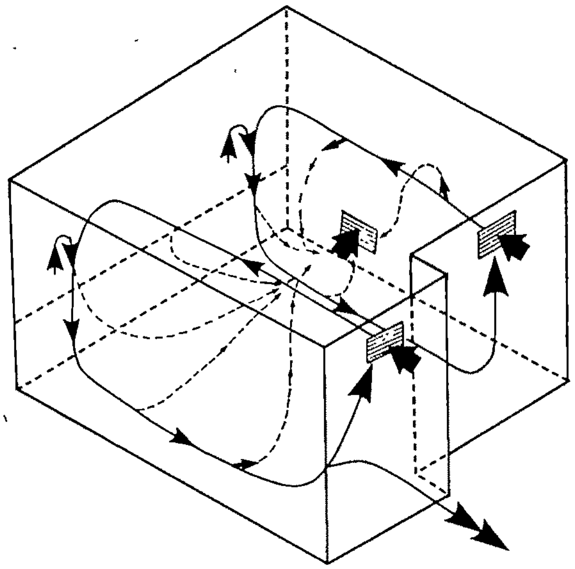

FIG. 5. Schematic diagram illustrating the distribution and mixing patterns of the major air currents in the outpatient theatre of the Birmingham Dental Hospital on a winter day with a room temperature of 22 °C, and an external air temperature of 3 °C.

The actual velocity vectors measured on a typical winter day during the contamination monitoring programme are shown in figure 6. On that day, the external air temperature was 3 °C and the theatre air temperature was 22 °C. The three main sources of air entering the theatre were from the two plenum ventilation entry grilles and a draught entering from the ill-fitting windows (nearest the reader on the left of figure 6). The way in which the windows closed caused the air inlet to be initially vertically upwards. However, about 0.3 m from the windows the air had adopted a downwards flow direction because of the higher density of the cold air compared with the room air. When doors and hatches are closed, air leaves the theatre via the plenum ventilation exhaust grille.

Obviously, the external air temperature is important in determining the magnitude of the large convection current and ultimately the movement of contaminants around the theatre. For example, when the theatre was revisited during a summer day when

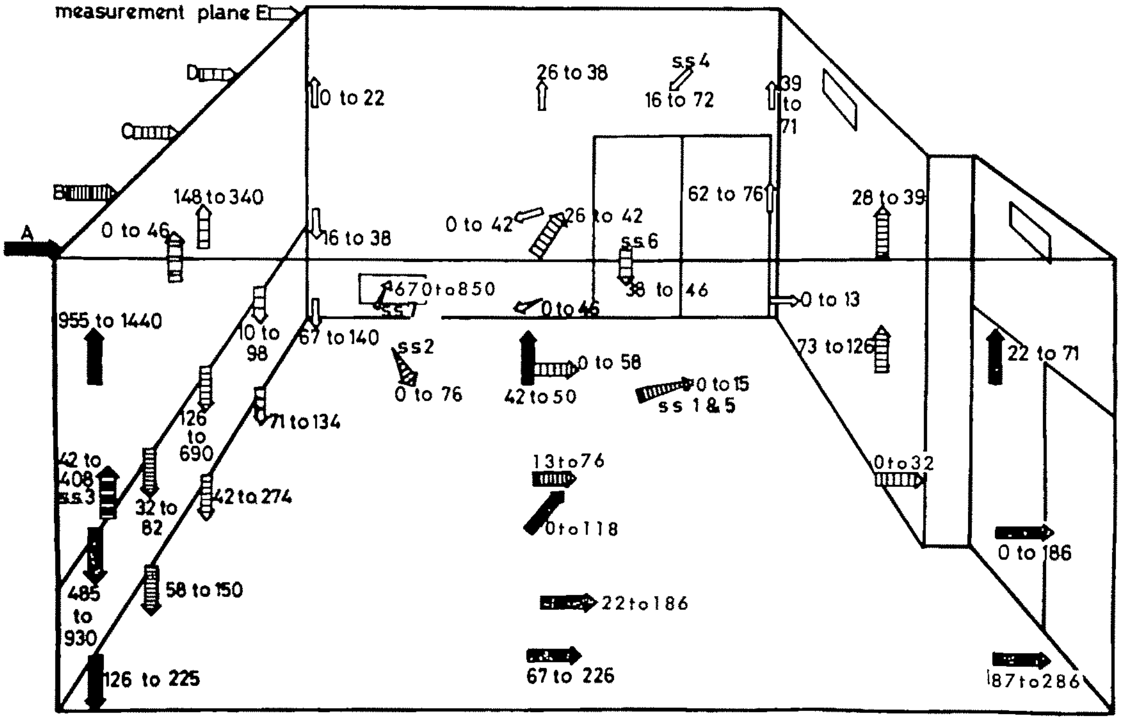

FIG. 6. The air movement vector pattern in the outpatient theatre of the Birmingham Dental Hospital on a winter day with a room temperature of 22 °C and an external temperature of 3 °C. The hot wire anemometer measurements are shown in mm s^{-1}; the range of air speeds and the approximate direction of the vector are shown for each measurement site. There are five main planes of measurement from the front to the back of the diagram and three planes from left to right. In addition, measurements were made at the seven fixed sample sites used for air contamination sampling: these are shown by the abbreviation ss.

the external air temperature was 19 °C no air movements faster than 50 mm s^{-1} could be found. Such results lead one to question the reliability of the plenum ventilation system, because air movement at 20 changes per hour would be expected to produce a greater movement of air than that measured on the summer day.

Some air contamination measurements seem well associated with the rate of turnover of fresh air at sample sites, others do not. Fixed site 3, for example, is on the window sill between anemometer measurement planes A and B (fig. 6), in a region where halothane and trichloroethylene contamination would be vigorously opposed by fresh air entry from the badly fitting windows and accordingly the median contaminant concentrations are significantly lower than elsewhere in the theatre.

Fixed sites 5 and 1 are both in still air close to the source of halothane, and at first glance their concentration readings are both significantly higher than fixed site 3, as one would expect. However, applying the statistical tests between sites 3 and 5 and 3 and 1 it is apparent that the only significant difference is that between sites 5 and 3. The difference between sites 1 and 3 is not significant. Because sites 1 and 5 are only 0.1 m apart this suggests that insufficient readings were taken to allow a statistically significant difference between sites 1 and 3 to emerge.

Blood halothane measurements

The number of measurements of blood halothane concentration from theatre personnel does not justify a rigorous statistical analysis. However, the mean uptake (± SD) of halothane into the blood during an operating session (morning or afternoon) may be summarized as follows: four dental students giving anaesthetics: 231 ± 81 μg $litre^{-1}$; three anaesthetists: 177 ± 50 μg $litre^{-1}$; combined sample of anaesthetists and students giving anaesthetics: 208 ± 49 μg $litre^{-1}$; three dental students performing extractions: 137 ± 57 μg $litre^{-1}$; two nurses: 57.1 ± 10.5 μg $litre^{-1}$. The halothane concentrations in the blood samples taken at the beginning of the sessions were all less than the expected instrumentation blank ± one standard deviation, except for two of the anaesthetists examined. One had been anaesthetizing in a morning session and had an initial blood halothane concentration of 47.1 μg litre^{-1}. The other had been on holiday for 1 week, but still had an initial halothane concentration of 31 μg litre^{-1}.

GENERAL DISCUSSION

If the risk to health from pollution by anaesthetic agents is difficult to quantify, exposure (which implies both atmospheric and blood concentrations) can be accurately and precisely measured, although the problems involved and the handling of the data so obtained are considerable if valid conclusions are to be drawn.

As an example, Mehta and others (1975) suggested, from limited data, that halothane contamination of theatre air is not localized to the area immediately around the anaesthetist, but is spread uniformly throughout the theatre. They suggested that all theatre staff are appreciably exposed to halothane, in a manner similar to the anaesthetists, but the results presented here show that anaesthetists and dentists are much more heavily exposed.

The present method of evaluating air contamination in an operating theatre is expensive in time, personnel and equipment, but it is essential if the various factors influencing air contamination are to be evaluated. A detailed knowledge of the fluctuations in air contaminant concentrations readily enables the causes of failure of contamination control systems to be determined.

If the requirement is only to monitor the average contaminant concentrations as part of a safety programme, then "personal monitor" systems are quite adequate and much cheaper (Davenport et al., 1976). Monitoring contaminant concentrations in expired air of theatre staff would be an alternative to the use of personal monitors, but would be more expensive than the latter.

In the light of knowledge gained in this work, it remains a matter of some concern that the D.H.S.S. circular (HC (76) 38) should have dismissed so lightly the possibility of improvements to the air conditioning system in operating theatres (which may have more beneficial effects than the tenuous benefit of reduction of contamination of the theatre air). The effect of standing near an unopened, singly-glazed window (site 3—fig. 4, table III) cannot be so lightly dismissed. As Göthe, Övrum and Hallen (1976) point out, the general level and pattern of ventilation of an operating theatre is a dominant factor in controlling the air contamination, but personal exposures of staff working close to the source of contamination may still need to be controlled by effective scavenging devices. The role of air movement in distributing the air contamination is clearly a subject worthy of much more detailed investigation than was possible here.

APPENDIX A

NON-PARAMETRIC STATISTICAL METHODS

The Kruskal–Wallis test

The data from all the fixed sites were pooled for the purpose of ranking the observations in order of increasing concentration. For all cases in which there were several observations at the same concentration value within experimental error (in statistical terminology, tied data), the ties were resolved by the well-established mid-rank method (Gibbons, 1976). All observations having the same concentration value were given the mean rank of those observations. Following these procedures the ranked data were re-allocated to their original groups so that the sum of the ranks for each sample population could be calculated. The rank sums thus obtained were used in calculating the Kruskal–Wallis H test statistic defined as:

$$H = \left(\frac{12}{N(N+1)} \sum_{j=1}^{k} \frac{R_j^2}{n_j}\right) - 3(N+1)$$

where k = number of sample populations (here the number of fixed sampling sites); R_j = the sum of ranks in the jth population; n_j = number of observations in the jth sample population and N = the total number of observations. Where there are many tied data, as here, the test statistic H must be corrected to make the corresponding P value more conservative. This is done by dividing H by the quantity:

$$1 - \left(\frac{\sum u^3 - \sum u}{N(N^2-1)}\right)$$

where u is the number of observations in all sample populations combined that are tied for any rank, and the sum $(\sum u^3 - \sum u)$ is over all sets of tied ranks. The number of degrees of freedom is the number of sample populations (k) minus one. The P value corresponding to the calculated H value is normally found as the right-tail probability from the chi-square distribution tables with $k-1$ degrees of freedom. This P value is the confidence limit for the null hypothesis that the medians of all the sample populations are the same. If the P value is very small, the null hypothesis is rejected and it may be confidently said that at least one median differs significantly from the others.

However, this general test does not identify which medians differ significantly from one another, so that a multiple comparison extension of this test must now be used (for example Dunn, 1964; Gibbons, 1976). The mean rank of each sample distribution ($\bar{R}_i$) is calculated and the absolute values of the differences between all pairs of such means are calculated ($|\bar{R}_i - \bar{R}_j|$), so that $k(k-1)/2$ comparisons may be made simultaneously. A level of significance P is chosen for rejection of the null hypothesis and P may be as large as 0.30 for rejection, because a large number of comparisons as distinct from a large number of observations are being made (Bradley, 1968; Hájek, 1969). The next step is to find the quantile point of the probability of $P/k(k-1)$, called the critical z value. When the null hypothesis is true the following inequality holds for all pairs of mean ranks $\bar{R}_i$ and $\bar{R}_j$

$$|\bar{R}_i - \bar{R}_j| \leq z\sqrt{\left[\frac{N(N+1)}{12}\left(\frac{1}{n_i}+\frac{1}{n_j}\right)\right]}$$

with a probability $(1-P)$.

The Kolmogorov–Smirnov two-sample test

The cumulative sample distribution functions are used for the test and for each concentration range the difference between the two cumulative distributions is calculated. The absolute values of the differences so obtained are compared with one another and the greatest absolute value is chosen as the test statistic for the two-sided version of the test. The test statistic is then compared with a theoretical test statistic for a particular P value. If the theoretical test statistic is exceeded, then the null hypothesis (that the distributions are the same at all concentration ranges) is rejected with the chosen P value. In the one-sided version of the test the sign of the difference enables one to distinguish which distribution median is larger.

Tests for randomness of data

The air contamination was sampled using an objective sampling scheme at regular 5-min intervals throughout each day. The events giving rise to air contamination were not at regular intervals during the day. Thus, it might be reasonable to expect that the contamination measured would be randomly distributed in time and no bias would arise from the experimental design. This was tested using a standard quality control test: the runs-up-and-down test (Gibbons, 1976). The results of such tests showed that the data were genuinely random and no bias could arise from non-randomness.

APPENDIX B

SIMPLE CORRELATION ANALYSIS

The results from the theatre record and the summed measurements of halothane and trichloroethylene concentrations for each morning or afternoon session were analysed by simple correlation analysis using the Statistical Analysis System of Barr and Goodnight (1972). This system was available as an ICL 1906 computer program package and the tests were performed by J. A. Lewis, F. Grady and A. Barker (personal communications). In the analysis, all significant tests were Fisher F tests, and it may be expected that some of the P values quoted in the discussion in the main text are optimistic, in view of the fact that not all of the variables tested were normally distributed. At the time these tests were performed no non-parametric versions of such tests were available to us.

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CONTAMINATION DE L'AIR AMBIANT DANS UNE SALLE D'OPERATIONS DENTAIRES PREVUE POUR LES MALADES DE CONSULTATION EXTERNE

RESUME

L'importance de la contamination de l'air par l'halothane au cours d'une session opératoire a été reliée au nombre de malades traités, à l'usage total que l'on a fait de l'halothane, au remplissage du vaporisateur et au nombre de malades à hyperventiler par session. La teneur en trichloroéthylène de l'air de la salle d'opération n'a correspondu qu'à l'usage total et au remplissage du vaporisateur. On a trouvé une très forte association personnelle ($P \leqslant 0,001$) entre l'anesthésiste et l'importance de la contamination de l'air par l'halothane. Cette association a été moins forte pour le trichloroéthylène ($0,05 < P < 0,1$). La contamination médiane de l'air ambiant par l'halothane à proximité des visages des anesthésistes et des chirurgiens-dentistes a été entre six et neuf fois plus grande que la contamination médiane de l'air aux lieux d'échantillonnage fixes ($P \leqslant 0,005$).

VERUNREINIGUNG DER UMGEBUNGSLUFT IN EINEM POLIKLINISCHEN ZAHNÄRZTLICHEN OPERATIONSSAAL

ZUSAMMENFASSUNG

Der Umfang an Luftverunreinigung durch Halothan während einer Operationssession wurde mit der Anzahl an Patienten, dem Gesamtverbrauch von Halothan, dem Nachfullen eines Zerstaubers und der Anzahl an hyperventilierenden Patienten pro Session in Zusammenhang gebracht. Der Trichloräthylengehalt der Saalluft stand nur mit dem Gesamtverbrauch und dem Nachfüllen eines Zerstäubers im Zusammenhang. Es wurde eine sehr starke Assoziation ($P \leqslant 0,001$) zwischen dem Narkosearzt und dem Ausmass an Luftverunreinigung mit Halothan festgestellt. Für Trichloräthylen war die Assoziation schwächer ($0,05 < P < 0,1$). Die mittlere Verunreinigung der Umgebungsluft mit Halothan war in der Nähe der Gesichter von Narkoseärzten und Zahnärzten zwischen sechs- und neun mal grosser als die mittlere Luftverunreinigung an den festen Probennahmestellen ($P \leqslant 0,005$).

CONTAMINACION DEL AIRE AMBIENTE EN UN QUIROFANO ODONTOLOGICO PARA PACIENTES NO HOSPITALIZADOS

SUMARIO

Se correlacionó la contaminación del aire por halotano durante una sesión de intervenciones con la cantidad de pacientes, el uso total de halotano, el relleno de un vaporizador y el número de pacientes hiperventilados por sesión. El contenido de tricloroetileno en el aire del quirófano se correlacionó solamente con el uso total y relleno de un vaporizador. Se descubrió una intensa asociación personal ($P \leqslant 0,001$) entre el anestesista y el grado de contaminación del aire con halotano. La asociación fue menos notable ($0,05 < P < 0,1$) en el caso de tricloroetileno. La contaminación del aire ambiente medio con halotano en las inmediaciones de las caras de los anestesistas y de los cirujanos dentales fue entre seis y nueve veces superior a la contaminación media del aire en los sitios de muestreo fijos ($P \leqslant 0,005$).

Br. J. Anaesth. (1979), **51**, 857

LAMINAR FLOW ENCLOSURE—A POSSIBLE RISK TO THE PATIENT

D. L. Edbrooke, T. J. I. Shaw and G. F. Karliczek

SUMMARY

A retrospective comparison was made between two groups of 50 adult patients who underwent open-heart surgery in an operating suite with two adjacent rooms, one of which was equipped with a laminar flow enclosure. Core and body surface temperatures were measured at 15-min intervals for the 1st h after commencement of surgery. Patients in a laminar flow enclosure showed a significantly greater decrease in core temperature with time. Possible means of counteracting this are suggested.

Laminar air flow was used as early as 1960 to produce a particle-free environment, necessary in the assembly of atomic weaponry (Whitfield, 1966).

More recently, the principle has been applied to reduce airborne contamination of wounds in operating rooms (Buchberg et al., 1975; Scott and Guthrie, 1975) and evidence now exists that a statistically significant reduction in wound infection occurs (Clark, 1973; Dankert, Eijgelaar and van der Waaij, 1976). It has been our impression that patients undergoing surgery in a cardiac theatre equipped with a laminar flow enclosure suffered a greater decrease in core temperature than a comparable group of patients undergoing surgery in an adjacent theatre not so equipped.

Ideally, in order to substantiate such observations it would have been desirable to perform a prospective study on two randomly selected groups of adult patients for open heart surgery, with and without the laminar flow enclosure, and using the same operating room. However, in view of the evidence of decreased wound contamination with the use of the laminar flow enclosure it was felt that such a prospective study was not justified ethically. Therefore, a retrospective study was made on two groups of patients who had undergone open-heart surgery in adjacent operating rooms.

PATIENTS AND METHODS

Between February and August 1978, 50 adult patients underwent cardiac surgery in the operating room with the laminar flow enclosure. Fifty similar patients underwent surgery between December 1977 and August 1978 in the alternative operating room which is not equipped with such an enclosure.

Control of the environment

The environment of the two adjacent rooms was controlled automatically to maintain a temperature of 20 °C and a humidity of 65% with 20 air changes every hour. The design of the operating rooms was essentially the same.

The laminar flow enclosure

The laminar flow enclosure (OPC 122–244 built by Pielkenrood-Vinitex B.V., Assen-Delft, Netherlands) extracts air from the operating room, filters it, and directs it in a horizontal laminar fashion from the foot of the table, towards the patients' head (Scott and Guthrie, 1975). There is no facility to heat or cool the filtered air. The heat generated by the fans is dissipated from the air intake of the enclosure and is controlled readily by the normal air conditioning system. The air flow produced was measured using a thermo-anemometer (TNO, Delft, Netherlands) and the velocity adjusted to 0.5 m s^{-1}.

Temperature measurement

Two precalibrated probes (Yellow Spring Instruments Series100; accuracy ±0.1 °C at working range, with Hewlett–Packard Recorders 78201 B) were used: a lower oesophageal probe to indicate core temperature (Whitby and Dunkin, 1969, 1971) and a skin probe attached to the thenar eminence of the left hand.

Methods of anaesthesia

In all patients anaesthesia was induced with etomidate 0.3 mg kg^{-1} after a standard premedication

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with diazepam, and anaesthesia was maintained with varying doses of fentanyl, and droperidol 0.1 mg kg^{-1}. Muscular relaxation was achieved with pancuronium 0.1 mg kg^{-1} and the lungs were ventilated (Servo 900B ventilator) to normocapnia, as indicated by a carbon dioxide analyser (Servo CO_2 analyser 930) and the results checked by arterial blood sampling.

The inspired oxygen and nitrous oxide mixture was humidified with a Bennett cascade humidifier (water bath adjusted to 40 °C). A standardized skin preparation with chlorhexidine 0.5% and draping with three layers of cotton was used. Crystalloid solutions (at room temperature) were infused at a rate of 5 ml kg^{-1} h^{-1} and any patient who received more than 8 ml kg^{-1} h^{-1} or less than 3 ml kg^{-1} h^{-1} was excluded from the study.

In addition, any patient receiving any drug affecting peripheral vascular tone other than those mentioned above was excluded.

Analysis of results

The following were recorded: age; surface area (du Bois formula); type of operation; change in oesophageal temperature from initial value at 15, 30, 45 and 60 min after commencement of surgery; change in skin temperature from initial value at 15, 30, 45 and 60 min.

Mean values and standard deviations (SD) were calculated and the results in both groups compared using Student's t test.

RESULTS

There was no significant difference in age ($t = 1.21$; $P > 0.05$) or surface area ($t = 1.47$; $P > 0.05$) between the two groups (table I). The numbers of patients in each group undergoing coronary artery bypass grafting and other cardiac operations (valve surgery, ASD and VSD closures) were analysed, since patients for coronary artery bypass surgery are draped in a different fashion from those undergoing valve surgery and septum closures, with exposure of both legs for dissection, there is thus a greater surface area of skin exposed to possible cooling. However, there were similar numbers in each group (table I).

TABLE I. *Age, surface area and numbers of patients undergoing coronary artery bypass surgery*

	Laminar	Non-laminar
Age (yr) (mean ± SD)	48.7 ± 13.5	45.2 ± 16.1
Surface area (m^2) (mean ± SD)	1.82 ± 0.15	1.74 ± 0.19
Coronary artery bypass grafts (%)	24 (48)	29 (58)
Total no. of patients	50	50

At the commencement of surgery the mean oesophageal temperatures of the two groups were 35.9 °C ± 0.7 (SD) for the laminar group and 36.1 °C ± 0.7 for the non-laminar group ($t = 1.21$; $P > 0.05$). Table II shows the changes in oesophageal and skin temperature at 30 min ($\delta_t 30$) and 60 min ($\delta_t 60$) from the commencement of surgery (values at 15 and 45 min not shown), and it may be seen that the oesophageal temperature in both groups decreased significantly at all times (table II and fig. 1).

The changes in skin temperature were not significant (table II).

DISCUSSION

Little attention has been focused on possible side-effects of laminar flow ventilation. When this type of ventilation is used, there is a significant increase in the general background noise in the operating room suite (Scott and Guthrie, 1975), and this may have a deleterious effect on the efficiency of staff (National

TABLE II. *Mean decreases in oesophageal and skin temperatures at* 30 *and* 60 *min* (± *SD*), t *values and probabilities* (P)

	Laminar		Non-laminar	
	$\delta_t 30$	$\delta_t 60$	$\delta_t 30$	$\delta_t 60$
Oesophageal temp. diff. (°C)				
Mean ± SD	−0.5 ± 0.3	−0.8 ± 0.5	−0.2 ± 0.5	−0.3 ± 0.5
t	3.7	5.6	3.7	5.6
P	< 0.001	< 0.001	< 0.001	< 0.001
Skin temp. diff. (°C)				
Mean ± SD	+0.3 ± 1.2	+0.6 ± 1.7	+0.4 ± 1.0	+0.6 ± 1.2
t	0.6	0.03	0.6	0.03
P	> 0.05	> 0.05	> 0.05	> 0.05

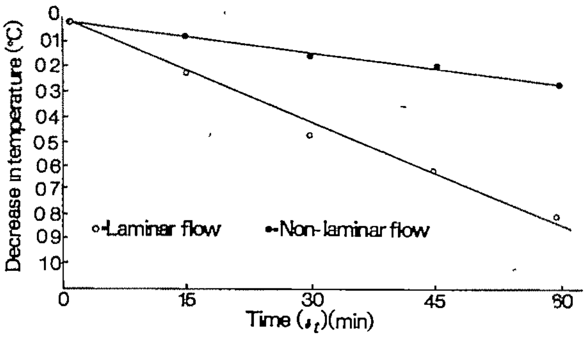

FIG. 1. Mean temperature decrease from the commencement of surgery.

Research Council, 1964). Laminar flow ventilation, however, also has a cooling effect on undraped areas of a patient. Moreover, it has been advocated that the use of this type of ventilation should be restricted to the types of surgery where operations are long and airborne wound contamination is more likely, for example orthopaedic, cardiac and vascular surgery (Whyte and Carson, 1970). Patients undergoing this type of surgery are likely to suffer a decrease in core temperature (Newman, 1971; Dyde and Lunn, 1970).

Temperature changes were studied in patients at the start of surgery in order to reduce the number of variables (such as infusion of cool solutions) to a minimum. Similar changes were found following the cessation of cardiopulmonary bypass although these are not documented. The mean rate of decrease in body temperature (0.2 °C in 1 h) in the non-laminar group is less than that found by Morris (1971), but our patients had a lower starting temperature as measurements began at the commencement of surgery and not of anaesthesia.

The mean rate of decrease in oesophageal temperature in the laminar flow group was more than twice that found in the non-laminar group, and the mean temperature after 1 h of measurement was 35.1 °C for the laminar, and 35.8 °C for the non-laminar group.

The skin temperatures of all patients increased following the commencement of surgery. This probably resulted from heat distribution to the periphery as a result of changes in peripheral vascular tone associated with anaesthesia. Too much emphasis cannot be placed on these figures, however, as the skin temperature was recorded at only one site (Shanks, 1975a).

Although in many of the patients the lungs were ventilated artificially at the cessation of nitrous oxide anaesthesia, in some the tracheal tube was removed and the patient permitted to breathe spontaneously. Decreases in core temperature of as little as 0.3 °C may be followed by shivering after operation (Roe et al., 1966), with an increase in oxygen consumption (Bay, Nunn and Prys-Roberts, 1968) at a time when cardiovascular and pulmonary function may not be optimal. For this reason, it is recommended that the core temperature of patients exposed to laminar flow during a lengthy procedure be recorded and active steps taken to prevent a decrease in temperature.

Prevention of a decrease in core temperature in the patient exposed to laminar flow

The patient should be positioned on a warming or heat-retaining mattress (Vale, 1973), taking care to avoid excessive temperature gradients and possible skin burns (Vale, 1972). Morris (1971) concluded that there was significant linear correlation between the patient's oesophageal temperature and the environmental temperature at intervals of 1, 2 and 3 h after induction of anaesthesia. The site of operation (intra-abdominal *v.* extra-abdominal) did not significantly affect this correlation. Increase of the operating room temperature to 24–26 °C with a humidity in excess of 55% will reduce or prevent a decrease in core temperature. However, this may be unacceptable to gowned members of the surgical team. Anaesthetic gases should be warmed and humidified, and cold fluids for i.v. infusion should be warmed to body temperature (Shanks, 1975b, c).

Finally, bedding should be warmed before transfer of the patient to the recovery or intensive treatment unit, in order to prevent heat loss at the end of anaesthesia (Holdcroft and Hall, 1978).

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ENCEINTE A ECOULEMENT LAMINAIRE—DANGER POTENTIEL POUR LES MALADES

RESUME

On a fait une comparaison rétrospective entre deux groupes de 50 malades adultes ayant subi une intervention chirurgicale à cœur ouvert dans une salle d'opérations comportant deux pièces adjacentes, dont l'une était équipée d'une enceinte à écoulement laminaire. On a pris la température du corps, en surface tout comme à l'intérieur, à intervalles de 15 min pendant la première heure de l'opération. Les malades se trouvant dans l'enceinte à écoulement laminaire ont accusé avec le temps une diminution importante de la température intérieure du corps. On suggère dans cet article plusieurs moyens possibles pour contrecarrer cet état de choses.

DIE LAMINARSTRÖMUNGSKAMMER—EINE MÖGLICHE GEFAHRENQUELLE FÜR DEN PATIENTEN

ZUSAMMENFASSUNG

Zwischen zwei Gruppen von 50 erwachsenen Patienten, die sich der Chirurgie am offenen Herzen unterzogen hatten in zwei aneinander grenzenden Operationssälen, von denen einer mit einer Laminarströmungskammer ausgestattet war, war ein retrospektiver Vergleich angestellt worden. Für die erste Stunde nach Beginn der Chirurgie wurden in 15-minütigen Abstanden die Kern- und Körperoberflachentemperaturen gemessen. Patienten in einer Laminarstromungskammer zeigten einen wesentlich grosseren Abfall in der Kerntemperatur über eine gewisse Zeitspanne. Es werden mögliche Mittel vorgeschlagen, um diesem entgegenzuwirken.

RECINTO DE FLUJO LAMINAR—UN POSIBLE RIESGO PARA EL PACIENTE

SUMARIO

Se llevó a cabo una comparación retrospectiva entre dos grupos de 50 pacientes adultos a quienes se practicaron operaciones de corazón abierto, en una sala de operación con dos cuartos adyacentes, uno de los cuales estaba equipado con un recinto de flujo laminar. Se midieron las temperaturas del núcleo y de la superficie del cuerpo, a intervalos de 15 min durante la primera hora después del comienzo de la operación. Los pacientes en el recinto de flujo laminar demostraron con el tiempo una reducción mucho mayor de la temperatura del núcleo. Se sugieren medios posibles para neutralizar esto.

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PLASMA CONCENTRATIONS OF ALPHAXALONE DURING CONTINUOUS INFUSION OF ALTHESIN

J. W. SEAR AND C. PRYS-ROBERTS

SUMMARY

Plasma concentrations of alphaxalone have been measured during various rates of continuous infusion of Althesin used to supplement nitrous oxide–oxygen anaesthesia in man. There was an approximately linear relationship between the plasma concentration of alphaxalone and the rate of infusion of Althesin. The rate of uptake of alphaxalone into the liver did not appear to be impaired in the presence of the steroid myoneural blocking agent pancuronium, or in patients with hepatic cirrhosis.

The use of a continuous i.v. infusion of Althesin for the maintenance of anaesthesia was described first by du Cailar (1972) and developed further by Savege and his colleagues (1975). The advantages of i.v. anaesthesia using Althesin are rapid awakening on cessation of the infusion, minimal cardiovascular depression and the elimination of the need for volatile anaesthetic gases. Several authors have described the clinical features of continuous Althesin anaesthesia.

Although a gas–liquid chromatographic method (GLC) for the measurement of the plasma concentration of alphaxalone was described by Child and colleagues (1972) and used by Dubois, Allison and Geddes (1975) to measure the plasma concentrations of alphaxalone after a single dose of Althesin, there have been no reports of the pharmacokinetics of continuous infusions of Althesin. We describe a study in which the alphaxalone concentrations in human plasma have been measured during various rates of continuous Althesin anaesthesia.

METHODS

Patients and anaesthetic management

The plasma concentrations of alphaxalone were measured during the continuous infusion of Althesin as a supplement to nitrous oxide–oxygen anaesthesia in 28 patients. Twenty-two patients without evidence of liver disease and six patients with cirrhosis of the liver were studied. The latter group of patients was undergoing surgery for the relief of portal hypertension. Some of the patients were also being studied independently to determine the cardiovascular effects of the infusions of Althesin. All patients were premedicated with papaveretum 15–20 mg i.m. 1 h before operation. Consent was obtained from every patient, after each had received an explanation of the nature of study.

Anaesthesia was induced with fentanyl 8 $\mu g\ kg^{-1}$ and Althesin (6–24 mg total steroid). The trachea was intubated following neuromuscular blockade with either pancuronium 0.1 $mg\ kg^{-1}$ or alcuronium 0.25 $mg\ kg^{-1}$, and the patients were ventilated artificially through a circle system without a soda-lime absorber, the fresh gas flow being adjusted to maintain Pa_{CO_2} within the range 5.1–5.6 kPa. Of the 22 normal patients, 12 received alcuronium and 10 received pancuronium. All of the patients with cirrhosis of the liver received pancuronium.

Anaesthesia was maintained with nitrous oxide 66% in oxygen, supplemented by Althesin administered as an infusion of 2.4 $mg\ ml^{-1}$ total steroid in Compound Sodium Lactate solution. The infusion rates of Althesin in this and the subsequent paper (Sear and Prys-Roberts, 1979) were multiples of a minimum rate of infusion (MIR) determined in a separate pilot study (Prys-Roberts, unpublished data) in 15 patients. These patients, like those in the present study, had been premedicated with papaveretum 15–20 mg, and were breathing spontaneously a mixture of nitrous oxide 66% in oxygen during inguinal herniorrhaphy. The minimum rate of infusion of Althesin in these patients which would just suppress movement in response to surgical stimulus ranged between 15 and 20 $\mu g\ min^{-1}\ kg^{-1}$ as the total steroid. In the present studies we used a nominal minimum infusion rate of Althesin of 18 $\mu g\ min^{-1}\ kg^{-1}$ (table

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II), which represents an infusion rate for alphaxalone of 13.5 μg min^{-1} kg^{-1}.

The infusion was established at this nominal rate for a period of 25–30 min to obtain a steady-state plasma concentration. Each patient had an arterial cannula in place to monitor the arterial pressure throughout surgery, thus all blood samples were withdrawn from this source. A sample of arterial blood was withdrawn to determine the plasma alphaxalone concentration at this nominal infusion rate.

Incremental increases in the rate of the Althesin infusion were made during the period of surgery and further blood samples withdrawn at 20–25-min intervals after each step change in the rate of infusion. By sampling blood at 5-min intervals after a step change of the infusion rate, we have determined that a steady concentration of alphaxalone in the plasma is achieved after 20 min. The plasma was separated within 2 h of collection of the samples, and stored at −20 °C until assayed for the alphaxalone concentration.

Assay of plasma alphaxalone concentration

The concentration of alphaxalone in plasma was measured by a GLC assay. It is possible also to measure alphadolone by GLC, but the sensitivity of the method is less than that for alphaxalone. Trimethyl silyl esters were formed using a modification of the method of Chambaz and Horning (1967).

To 1 ml of plasma, a known amount of internal standard, β-alphaxalone (3β-hydroxy,-5α-pregn-16-ene-11, 20 dione), was added, with 0.5 ml of 2.5% w/v NaOH. Ten millilitre of freshly distilled diethyl ether was used to extract the drug by manually shaking the test tube for 30 s. The ethereal layer was taken and evaporated to dryness.

Reference standards of alphaxalone were obtained by adding known amounts of drug to blank plasma and extracting as for the plasma samples. The silylation reagent consisted of N,O bis-trimethylsilyl acetamide, pyridine and trichloromethylsilane (100 vol : 20 vol : 1 vol). Twenty microlitre of this mixture was added to the dried extracts and incubated for 15 min at 50 °C. Samples were injected on to a Perkin Elmer F11 gas chromatograph containing a column of 3% OV 17, and using a flame ionization detector. The oven temperature was 250 °C, injection temperature 260 °C and detector temperature 300 °C. Nitrogen 45 ml min^{-1} was used as the carrier gas.

For each patient, a blood sample obtained before anaesthesia was assayed in a similar manner, as a small interference peak with retention characteristics identical to those of alphaxalone has been observed in the plasma of some patients.

Using a 1-ml sample of plasma, a linear relationship between the alphaxalone concentration and flame ionization detector response has been found over the clinical range 100 ng ml^{-1} to 10 μg ml^{-1}. Repeated analysis of separate samples gave a mean coefficient of variance of 7.87%. The chemical nature of the measured peak, namely trimethylsilyl alphaxalone, has been confirmed using gas chromatograph : mass spectroscopy (GC : MS). No chromatographic interference has been seen from any other of the anaesthetic drugs used.

RESULTS

In every patient, there was an approximately linear relationship between the alphaxalone concentration in the plasma and the rate of infusion of alphaxalone. Linear regression analysis was used to determine the regression equation for each patient between the plasma concentration of alphaxalone and the infusion rate of alphaxalone ($r > 0.9$; $P < 0.01$).

Table I shows the values for the mean slope of the regression equation between the plasma concentration of alphaxalone and the rate of infusion of alphaxalone for the 22 normal patients and six patients with cirrhosis of the liver. There was no statistical difference between the slopes of the mean regression lines for the 12 patients who received alcuronium and the 10 who received pancuronium. The patients with cirrhotic liver disease showed a similar relationship between the plasma concentration of alphaxalone and the rate of infusion of alphaxalone, although the mean value for the slope of the regression line was significantly less than that in normal subjects ($t = 3.579$; $P < 0.002$).

TABLE I. *Slope of regression equation (mean ± SEM) of plasma concentration of alphaxalone against rate of infusion of Althesin (fig. 1). *Difference between patients receiving alcuronium and patients receiving pancuronium: not significant; †difference between all 22 normal patients and six patients with cirrhosis of the liver*: $t = 3.579$; $P < 0.002$

Patients	Slope of regression equation
Normal (n = 22)	0.034 ± 0.004
12 receiving alcuronium	0.037 ± 0.006 } *
10 receiving pancuronium	0.030 ± 0.003 }
With cirrhosis of liver (n = 6)	0.018 ± 0.002†

Because of small variations in the infusion rates of Althesin within the patients studied, we have grouped plasma concentrations of alphaxalone in relation to infusion rates of alphaxalone close to the multiples of the nominal infusion rate. The results are shown in table II, in which it can be seen that a fivefold increase in the rate of infusion causes the plasma concentration of alphaxalone to be approximately doubled.

TABLE II. *Plasma concentration of alphaxalone at varying rates of infusion of Althesin (mean ± SEM)*

Rate of infusion (μg min^{-1} per kg)		Plasma concn of alphaxalone (μg ml^{-1})
Althesin	Alphaxalone	
18 ± 0.9	13.5 ± 0.66	1.91 ± 0.09
36 ± 0.8	26.7 ± 0.63	2.24 ± 0.15
52 ± 1.0	38.7 ± 0.77	2.86 ± 0.17
69 ± 1.6	51.9 ± 1.22	3.28 ± 0.09
90 ± 3.2	67.8 ± 2.41	3.93 ± 0.28

Figure 1 shows the values for the 22 normal patients of the mean plasma alphaxalone concentration at various rates of infusion of alphaxalone, and the individual values of plasma concentration of alphaxalone in the six patients with cirrhosis of the liver. The plasma concentration of alphaxalone for a given infusion rate was lower in the patients with cirrhosis of the liver than in the group of patients with normal liver function.

DISCUSSION

In man, it is believed that there is a rapid uptake of the constituents of Althesin, alphaxalone and alphadolone, from the blood into the liver, and perhaps muscle and kidney. In the liver, alphaxalone is probably metabolized by microsomal enzymes, and then conjugated to a glucuronide which is excreted in the bile. Strunin and co-workers (1977) studied the pharmacokinetics of alphaxalone in the blood following the injection of a single dose (10–20 μCi) of ^{14}C-labelled alphaxalone. In both healthy patients and those with obstructive bile duct disease, Strunin and colleagues were able to show a triphasic decay pattern of the plasma radioactivity. Fifty-nine per cent of the radioactivity appeared in the urine within 24 h in the healthy patient. In the patients with obstructive biliary disease, only 38% appeared in the urine within the same time. This suggests that the water-soluble glucuronide conjugates of alphaxalone or its metabolites are reabsorbed in the small intestine and excreted in the urine. Gas chromatography may be coupled with mass spectroscopy to detect specific mass fragments. Using this technique, alphadolone, unchanged alphaxalone and its reduced metabolite, $3\alpha,20\xi$di hydroxy 5αpregnane, have been detected in the urine of both normal patients and those with cirrhotic liver disease (H. Makin and J. Sear, unpublished data).

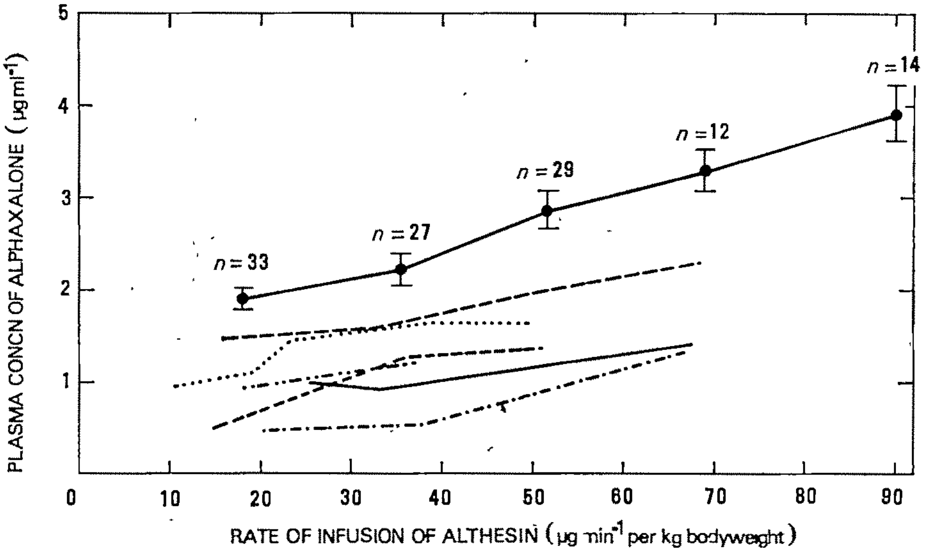

FIG. 1. Mean (± SEM) plasma alphaxalone concentrations at various rates of infusion of Althesin in 22 normal patients, and the individual values of the plasma concentration of alphaxalone in six patients with cirrhosis of the liver.

The slope of the regression equation between the plasma concentration of alphaxalone and the infusion rate of alphaxalone may be taken as an index of drug uptake into the liver. From our results, there appears to be linear uptake over the range of rates of infusion studied. There is no evidence of any decreased uptake of alphaxalone in the patients with cirrhotic liver disease; indeed our results would suggest that alphaxalone uptake may be enhanced in cirrhosis.

In the group of patients with cirrhotic liver disease, there was a lower plasma concentration of alphaxalone for a given rate of infusion of alphaxalone when compared with the control values. This may be explained in several ways. In cirrhosis of the liver, there is usually an accompanying hepatosplenomegaly until end-stage cirrhosis is reached. Thus, the volume of distribution of any drug within the hepatic circulation is enlarged, with an increase in drug sequestration. This leads to an effective increase in the rate of clearance of the drug by the liver. Similarly, there may be abnormalities of the hepatosplenic vasculature, such as arterio-venous shunts. These also may facilitate drug clearance. The role of the plasma proteins in drug binding may affect the amount of free drug in the blood. Alphaxalone has been shown to bind with high affinity to albumen and β-lipoproteins (Jones, 1972). Although the former are decreased usually in cirrhotic liver disease, the β-lipoproteins may increase in biliary cirrhosis, so increasing the amount of bound alphaxalone. A similar high affinity binding of alphaxalone has been demonstrated for the IgG immunoglobulins. These immunoglobulins exist both intravascularly and in the extracellular fluid. Both of these protein pools increase in cirrhosis of the liver, and the latter may act as a ready source for drug binding and sequestration.

The data presented here would suggest that a reduction in the dose of Althesin in chronic liver disease may not be necessary, in view of the apparent ability of the liver to clear the drug adequately. In each of the six patients, there was no prolongation of recovery time compared with the normal group. This is in contrast to the experience of du Cailar (1972), who observed a prolonged recovery of up to 2 h in two patients with hepatic failure. An impairment of radiolabelled alphaxalone clearance from the plasma has been seen also by Ward, Adu-Gyamfi and Strunin (1975) in a patient in acute hepatic failure.

Pancuronium is a quaternary ammonium-substituted steroid with non-depolarizing neuromuscular blocking properties. The uptake of many steroids into tissues depends on their combination with a specific cellular receptor molecule. The data presented here may indicate that there is no competition between pancuronium and alphaxalone for the same tissue uptake mechanism. The alternative hypothesis is that there is an adequate reserve receptor capacity within these tissues. If pancuronium was to inhibit the uptake of alphaxalone, it would be seen as an increase in the slope of the regression line between the plasma alphaxalone concentration and the infusion rate of alphaxalone. This has not been observed in our patients.

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CONCENTRATIONS D'ALPHAXALONE DANS LE PLASMA PENDANT UNE INFUSION CONTINUE D'ALTHESINE

RESUME

On a mesuré les concentrations d'alphaxalone dans le plasma pendant l'infusion continue d'althésine, à différents débits, utilisée pour compléter chez l'homme l'anesthésie induite à l'aide d'oxygène-protoxyde d'azote. Il y a eu une relation à peu près linéaire entre la concentration d'alphaxalone dans le plasma et le taux d'infusion de l'althésine. Le taux de fixation de l'alphaxalone dans le foie n'a pas semblé être gêné en présence du pancuronium, agent de blocage stéroide myoneural, ou chez les malades souffrant d'une cirrhose du foie.

ALPHAXALONKONZENTRATIONEN IM BLUTPLASMA WÄHREND UNUNTERBROCHENER ALTHESININFUSION

ZUSAMMENFASSUNG

Es wurden die Alphaxalonkonzentrationen im Blutplasma bei verschiedenen Raten ununterbrochener Althesininfusion, zur Ergänzung der Lachgas/Sauerstoffnarkose im Menschen eingesetzt, gemessen. Zwischen der Alphaxalonkonzentration im Blutplasma und der Althesininfusionsrate bestand ein annähernd lineares Verhältnis. Die Aufnahmegeschwindigkeit von Alphaxalon in die Leber schien in der Gegenwart des neuromuskulären Blockierungssteroiden Pankuronium oder bei Patienten mit Leberzirrhose nicht beeinträchtigt zu sein.

CONCENTRACIONES DE ALFAXALONA EN EL PLASMA DURANTE INFUSION CONTINUA DE ALTESINA

SUMARIO

Se midieron las concentraciones de alfaxalona en el plasma durante varios ritmos de infusión continua de Altesina, utilizada para suplir la anestesia oxígeno-óxido nitroso en el hombre. Existía una relación aproximadamente lineal entre la concentración de alfaxalona en el plasma y el ritmo de infusión de Altesina. El ritmo de captación de alfaxalona dentro del hígado no pareció ser trastornado en presencia del pancuronio, agente bloqueador mioneural esteroide, ni tampoco en pacientes con cirrósis hepática.

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DOSE-RELATED HAEMODYNAMIC EFFECTS OF CONTINUOUS INFUSIONS OF ALTHESIN IN MAN

J. W. SEAR AND C. PRYS-ROBERTS

SUMMARY

The cardiovascular effects of infusions of Althesin at various rates to supplement nitrous oxide anaesthesia have been studied in seven spontaneously breathing patients and 11 patients ventilated artificially to normal Pa_{CO_2}. During spontaneous breathing, increasing rates of Althesin infusion were associated with increases in heart rate and cardiac output. The modest decrease in arterial pressure (-5%) was the result of a decrease in vascular resistance. Increasing rates of Althesin infusion were associated with increasing values of Pa_{CO_2}. During artificial ventilation, increasing rates of Althesin infusion (up to eight times the minimum infusion rate) caused dose-dependent decreases of arterial pressure and systemic vascular resistance, whereas heart rate and cardiac output were increased slightly at all rates of infusion.

Althesin (Glaxo Laboratories Ltd), a steroid anaesthetic agent containing alphaxalone and alphadolone acetate, may be used for both the induction and maintenance of anaesthesia. The cardiovascular effects of Althesin, used as a single dose for the induction of anaesthesia, have been described as decreases in arterial pressure, stroke volume, systemic vascular resistance and central venous pressure, while cardiac output is increased slightly as a result of a compensatory tachycardia (Campbell et al., 1971; Foëx and Prys-Roberts, 1972; Prys-Roberts, Foëx and Biro, 1972; Savege et al., 1972; Sonntag et al., 1973). The haemodynamic changes in patients receiving Althesin as a continuous i.v. infusion have not been described in such detail (du Cailar, 1972; Savege et al., 1975; Dechêne, 1977; Dunn et al., 1978), and no reports concerning dose-response effects have appeared. In this paper, we describe the cardiovascular effects of various rates of infusion of Althesin as a supplement to nitrous oxide anaesthesia in man.

METHODS

Eighteen patients (mean age 59 yr, mean weight 65.4 kg) undergoing peripheral arterial surgery received an infusion of Althesin to supplement nitrous oxide–oxygen anaesthesia. Consent was obtained from all the patients, and the nature of the studies to be undertaken was explained. Seven of the patients breathed spontaneously, while the remaining 11 patients were ventilated artificially to maintain Pa_{CO_2} 5.3 kPa. All of the patients were premedicated with papaveretum 15–20 mg i.m. 1 h before operation.

Spontaneously breathing patients

In these patients anaesthesia was induced with Althesin 36–48 mg and endotracheal intubation was performed after the administration of suxamethonium 1 mg kg^{-1} and the application of topical analgesia to the larynx and trachea using lignocaine 4%. Anaesthesia was maintained with nitrous oxide 66% in oxygen delivered through a Magill circuit, supplemented by Althesin as an infusion of 2.4 mg ml^{-1} total steroid in Compound Sodium Lactate B.P. The infusion rate was set initially at 18 μg kg^{-1} min^{-1}, defined in the previous paper (Sear and Prys-Roberts, 1979) as the minimum rate of infusion (MIR) which, under the conditions described, would just suppress movement in response to the surgical stimulus. This rate of infusion was maintained for 30 min by which time a steady state of cardiovascular variables was achieved in all patients, and a set of haemodynamic measurements was recorded. Samples of arterial blood were withdrawn for measurement of the plasma concentrations of alphaxalone and the estimation of blood-gas tensions. The rate of infusion of Althesin was then increased by multiples (2, 3 and 4) of this minimum infusion rate. Twenty minutes after each stepwise increase in the infusion rate a further set of haemodynamic measurements was recorded, and additional samples of arterial blood were withdrawn

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for determination of the plasma concentrations of alphaxalone and blood-gas analysis.

Artificially ventilated patients

In this group of patients, anaesthesia was induced with fentanyl 8 μg kg^{-1} followed by Althesin 12–24 mg, and endotracheal intubation was performed after the administration of pancuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with nitrous oxide 66% in oxygen delivered from a Penlon–Oxford ventilator set to provide a tidal volume of 15 ml kg^{-1} at a frequency of 12 b.p.m. using a semi-closed circuit without a soda-lime absorber. The fresh gas flow was adjusted to maintain Pa_{CO_2} within the range 5.1–5.6 kPa. The infusion of Althesin was commenced at 18 μg kg^{-1} min^{-1} (MIR). A single arterial sample was withdrawn after a period of 30 min to check the blood-gas values. A set of haemodynamic measurements was recorded 30 min after the commencement of the Althesin, after it had been ascertained that a steady state of circulatory variables existed. The infusion rate of Althesin was increased stepwise in multiples of MIR (2, 3, 4, 6 and 8). The order of the changes was varied from patient to patient, and sets of haemodynamic measurements were made 20 min after each step change of the rate of infusion.

In all patients intra-arterial (brachial), central venous (superior vena cava) and peripheral venous cannulae were placed under local analgesia before the induction of anaesthesia. The arterial pressure, central venous pressure, heart rate and e.c.g. were recorded continuously. The cardiac output was measured by the dye dilution technique using indocyanine green (Prys-Roberts, 1969). Values of cardiac output were standardized for a body weight of 70 kg, and derived values of stroke volume, systemic vascular resistance and rate–pressure product (systolic arterial pressure × heart rate) were calculated by standard formulae.

The statistical analysis of the haemodynamic measurements was carried out using two-way analysis of variance, and Student's paired and unpaired *t* tests.

RESULTS

Spontaneously breathing patients

The blood-gas values at the different multiples of MIR for the seven spontaneously breathing patients are shown in table I. As the rate of infusion of Althesin increased, there was an increase in Pa_{CO_2} as a result of the depressant effect of the Althesin on ventilation. The pH changes represent a pure respiratory acidosis in response to the increases in Pa_{CO_2}.

Figure 1 shows the effect of various rates of infusion of Althesin on the systolic arterial pressure (SAP), cardiac output ($\dot{Q}_{70}$) and derived value of systemic vascular resistance (SVR) in the seven patients breathing spontaneously. The cardiovascular variables are expressed as a percentage of the value at 1 MIR. The actual mean values at 1 MIR were SAP 125 mm Hg (SEM ± 6.7); cardiac output 4.41 litre min^{-1} per 70 kg (SEM ± 0.41); and SVR 1653 dyn s cm^{-5} (SEM ± 113). As the rate of infusion of Althesin was increased, there was a moderate decrease in the systolic arterial pressure as a result of a reduction in the systemic vascular resistance by a maximum of 12% (not significant). Despite the decrease in the systolic arterial pressure, the cardiac output was maintained at the slower rates of infusion and increased as the rate of infusion of Althesin was increased to 4 MIR (not significant). Figure 2 shows the relationship between the cardiac output ($\dot{Q}_{70}$), stroke volume (SV_{70}) and heart rate (HR). The actual mean values at 1 MIR were stroke volume 65.4 ml per 70 kg (SEM ± 2.9) and HR 69 beat min^{-1} (SEM ± 5.3). The maintenance and subsequent increase in the cardiac output was associated with an increase in heart rate (not significant at either 3 MIR or 4 MIR). The mean

TABLE I. *Blood-gas values (mean ± SEM) at different multiples of MIR for the spontaneously breathing patients* (n = 7). 1 *MIR represents an Althesin infusion rate of* 18 *μg* kg^{-1} min^{-1}. *Statistical significance using Student's paired* t *test*: *$P < 0.05$; **$P < 0.01$; ***$P < 0.01$; *n.s. = not significant*

	1 MIR	2 MIR	3 MIR	4 MIR
Hydrogen ion concentration (nmol $litre^{-1}$)	40.2 ± 1.0	41.4 ± 1.2 n.s.	43.7 ± 0.8 *	51.9 ± 5.2 *
Pa_{CO_2} (kPa)	5.7 ± 0.04	6.0 ± 0.1 *	6.6 ± 0.1 ***	7.0 ± 0.1 ***
Pa_{O_2} (kPa)	14.2 ± 0.8	13.6 ± 0.6 n.s.	14.2 ± 1.0 n.s.	12.7 ± 0.4 n.s.

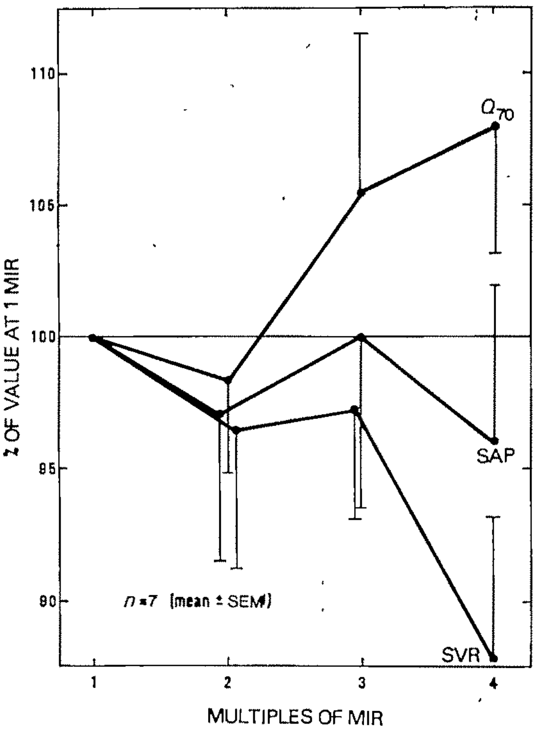

FIG. 1. Effect of various rates of infusion of Althesin on systolic arterial pressure (SAP), cardiac output (Q_{70}) and systemic vascular resistance (SVR) in seven patients breathing spontaneously.

values for stroke volume showed no significant changes throughout the study.

Artificially ventilated patients

Mean Pa_{CO_2} at the end of 30 min infusion of Althesin at 1 MIR in the 11 patients being ventilated artificially was 5.35 kPa (SEM ± 0.15) and mean pH 7.41 (40.6 nmol litre^{-1}, SEM ± 0.9). Figure 3 shows the change in SAP, Q_{70}, HR, SVR and SV_{70} at infusion rates up to 8 MIR. The mean values at 1 MIR were SAP 131 mm Hg (SEM ± 5.2); Q_{70} 4.0 litre min^{-1} per 70 kg (SEM ± 0.25); HR 75.5 beat min^{-1} (SEM ± 5.4); SVR 2081 dyn s cm^{-5} (SEM ± 144); SV 54.6 ml per 70 kg (SEM ± 2.5). As with the spontaneously breathing patients, there was a modest decrease in the systolic arterial pressure as the rate of infusion was increased. The maximum reduction was 17% at 6 MIR ($t = 2.918$; $P < 0.05$). Again, this was the result of a proportional decrease in the systemic vascular resistance ($t = 5.151$; $P < 0.01$). The cardiac output was well maintained slightly above the control value at 1 MIR, despite the increased rate of infusion of Althesin. This was largely caused by the increase in heart rate, although this did not reach statistical significance. There was no significant change in the stroke volume.

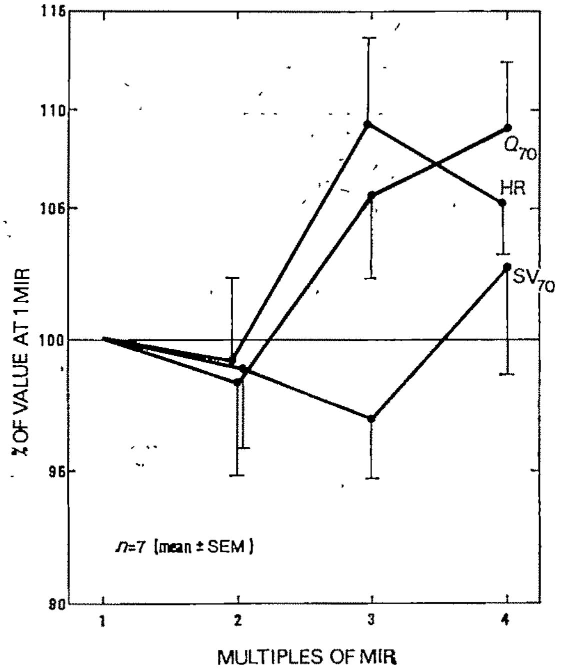

FIG. 2. Effect of various rates of infusion of Althesin on cardiac output (Q_{70}), stroke volume (SV_{70}) and heart rate (HR) in seven patients breathing spontaneously.

The percentage decrease in systemic vascular resistance for increasing rates of infusion of Althesin was similar in both the spontaneously breathing and artificially ventilated groups of patients.

Table II shows the systolic arterial pressure–heart rate product for multiples of MIR in both the spontaneously breathing and artificially ventilated patients. There were only modest and statistically insignificant changes in the SAP–HR product despite up to an eightfold increase in the rate of infusion of Althesin. The decrease in arterial pressure correlated significantly ($r = 0.92$; $P < 0.01$) in both groups of patients with the increase in plasma concentration of alphaxalone.

Recovery in all of the patients studied was not prolonged, indicating the non-cumulative property of infusions of Althesin.

TABLE II. *Systolic arterial pressure × heart rate product at varying rates of infusion of Althesin (mean ± SEM). 1 MIR represents an infusion rate of 18 μg kg^{-1} min^{-1}. None of the values reach statistical significance compared with values at 1 MIR*

Ventilation	1 MIR	2 MIR	3 MIR	4 MIR	6 MIR	8 MIR
Spontaneous	8506	8195	9455	8753	—	—
($n = 7$)	±885	±1100	±2233	±1797		
Artificial	9768	9525	10 854	10 224	8807	9290
($n = 11$)	±937	±698	±1379	±1088	±954	±2022

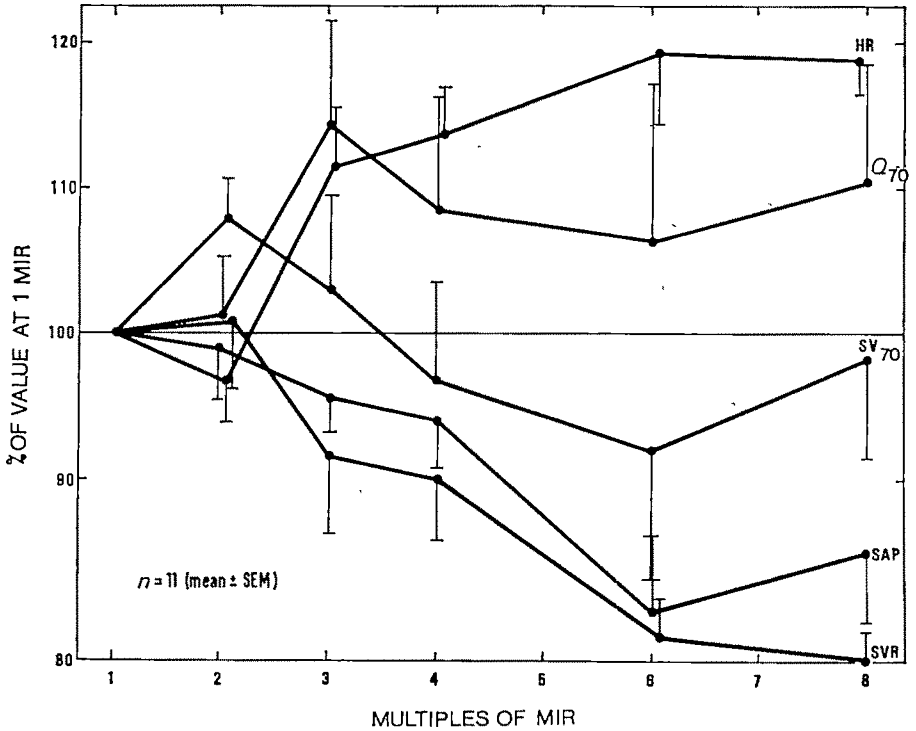

FIG. 3. Effect of various rates of infusion of Althesin on systolic arterial pressure (SAP), cardiac output (Q_{70}), heart rate (HR), systemic vascular resistance (SVR) and stroke volume (SV_{70}) in 11 patients being ventilated artificially to mean Pa_{CO_2} of 5.35 kPa. Note that the scale of percentage changes differs from those in figures 1 and 2.

DISCUSSION

The results of this study show the inherent cardiovascular stability associated with infusions of Althesin when used for the maintenance of anaesthesia. We have shown here that the rate of infusion of Althesin in relatively elderly patients may be increased up to eight times the minimum infusion rate as defined previously (Sear and Prys-Roberts, 1979) with only a small decrease in the mean arterial pressure. This is consistent with the high therapeutic index for Althesin following its use as a bolus dose for the induction of anaesthesia (Child et al., 1971). A fivefold increase in the infusion rate of Althesin results in an approximate doubling of the plasma concentration of alphaxalone. By contrast, a twofold increase in the minimum alveolar concentration (MAC) of most volatile agents would cause a much greater decrease of the arterial pressure, even in healthy young volunteers (Eger et al., 1970).

Our minimum rate of infusion of Althesin is less than that quoted by some other authors for the maintenance of anaesthesia (du Cailar, 1972; du Cailar et al., 1975; Savege et al., 1975; de Bellis and Bertieri, 1976; Hachet and Biro, 1976; Dechêne, 1977; Laurent and du Cailar, 1977; Pesce and Strambi, 1977; Dunn et al., 1978), although there are several differences between our patients and those studied by these authors. Apart from variations in premedication, several describe techniques involving the simultaneous infusion of Althesin with a narcotic drug. Savege and colleagues (1975) used an average infusion rate of 81 μg min^{-1} per kg body weight of alphaxalone in their patients, who were either breathing spontaneously or being ventilated with oxygen-enriched air.

Minimum alveolar concentration (MAC) has been proposed as a standard of equipotency for volatile and gaseous anaesthetics (Eger, Saidman and Brandstater, 1965), and a number of reports concerning the cardiovascular effects of these agents have been based on the "dose-response" relationship in which the effects of increasing concentrations of the agent have been multiples of MAC (Eger et al., 1970). The advantage of the MAC concept is based on the relationship of alveolar concentration to the blood concentration of the gas or volatile agent. To our knowledge, no one has suggested that a similar standard of equipotency might be applied to anaesthetic drugs administered by continuous i.v. infusion. We have defined, *for the purposes of this study*, the minimum infusion rate (MIR) for Althesin as that which would completely suppress movement in response to a surgical stimulation in each individual patient. It is advantageous to have a threshold dose of this nature as the basis of comparative cardiovascular studies, although it is important also to relate this constant rate of administration of a drug to the plasma concentration. This represents a standard degree of suppression of a neurophysiological response—that to a painful stimulus. There is merit in relating this standard to a clinical end-point rather than using a pharmacological definition such as the dose (or rate of administration) which will suppress movement in 50% of patients (ED_{50}).

It is convenient in describing dose-response studies to use simple multiples of a minimum dose (or rate of administration). In terms of anaesthesia, one cannot utilize less than a full anaesthetizing dose of an agent, but it is important to bear in mind that by doubling or trebling the minimum dose, one does not necessarily double or treble the neurophysiological effect. Nevertheless, the relationship between increasing rates of administration of a drug, whether volatile or i.v., and the impairment of cardiovascular performance is important as a means of defining the acute toxicity of the drug. Thus, in this and the previous paper (Sear and Prys-Roberts, 1979), we define our nominal MIR simply as a starting point for a study of increasing rates of administration of Althesin. There is clearly scope for defining MIR values for Althesin infusions given alone, with nitrous oxide-oxygen mixtures, and with other drugs such as opiates.

Because Althesin is not a pure compound, but a mixture of two steroid anaesthetics of different potencies, it is difficult to be pharmacologically precise in a study of this nature. We have chosen to express the cardiovascular effects in two ways, in relation to the rate of administration either of the drug mixture or of its main active constituent, alphaxalone. In the previous paper, we correlated the plasma concentration of alphaxalone to various rates of administration of the total steroid mixture, Althesin.

In the present study, we used as a nominal starting point an infusion rate (1 MIR) of 18 μg kg^{-1} min^{-1}. It is interesting to compare the values of pressure and flow-related variables in the patients in this study (table III) with those under comparable conditions in similar patients during nitrous oxide anaesthesia with spontaneous ventilation, and under nitrous oxide-relaxant anaesthesia with artificial ventilation (Prys-Roberts et al., 1967).

Increasing the rate of infusion of Althesin caused decreases in systolic and diastolic arterial pressures as a result of a decrease in the systemic vascular resistance, while cardiac output was maintained at the lower rates of infusion but increased at higher infusion rates because of the accompanying tachycardia. Similar haemodynamic effects have been observed following the administration of single doses of Althesin for the induction of anaesthesia (Campbell et al., 1971; Savege et al., 1973; Sonntag et al., 1973). By contrast, Savege and colleagues (1976) were unable to show any significant effect of either the first or the second doses of Althesin 50 μl kg^{-1} on the heart rate in premedicated patients before cardiac surgery. It is interesting to note that most studies have observed a reduction in the stroke volume following the induction of anaesthesia with Althesin. In both the spontaneously breathing patients and those being ventilated artificially to constant Pa_{CO_2}, there was no significant change in the stroke volume at any of the rates of infusion of Althesin. Thus, the main effect of Althesin on the cardiovascular system is by decreasing the systemic vascular resistance. Changes in the systolic arterial pressure × heart rate product may be taken as an index of changes in the myocardial oxygen

TABLE III. *Comparison of haemodynamic pressure and flow-related variables (mean ± SEM) in the patients in this study, and those under comparable conditions during nitrous oxide anaesthesia (Prys-Roberts et al., 1967). Values reaching statistical significance using Student's unpaired* t *test*: *P < 0.02; **P < 0.01; *n.s. = not significant*

	Heart rate (beat min^{-1})	Mean arterial pressure (mm Hg)	Cardiac output (litre min^{-1} per 70 kg)	Stroke vol. (ml per 70 kg)	Systemic vascular resistance (dyn s cm^{-5})	Pa_{CO_2} (kPa)
Spontaneous ventilation						
Prys-Roberts (n = 14)	64 ± 3.5	81 ± 2.3	4.43 ± 0.12	69 ± 5	1470 ± 51	6.08 ± 0.2
Present study (n = 7)	69 ± 5.3 n.s.	92 ± 9.5 n.s.	4.41 ± 0.41 n.s.	65 ± 3 n.s.	1653 ± 113 n.s.	5.66 ± 0.4 n.s.
Artificial ventilation						
Prys-Roberts (n = 13)	63 ± 3.6	88 ± 2.3	4.09 ± 0.21	64 ± 5	1598 ± 106	6.10 ± 0.2
Present study (n = 11)	76 ± 5.4 n.s.	94 ± 4.8 n.s.	4.00 ± 0.25 n.s.	55 ± 3 n.s.	2081 ± 144 *	5.35 ± 0.15 **

consumption (Nelson et al., 1974). Our results indicate that only minor variations occur in the utilization of oxygen by the myocardium despite eightfold increases in the rate of infusion of Althesin.

Dunn and co-workers (1978) have observed an increase in the minute volume and respiratory rate of patients breathing spontaneously during nitrous oxide–oxygen anaesthesia supplemented by an infusion of Althesin. However, from the data from our spontaneously breathing group of patients, it will be seen that increases in the rate of infusion of Althesin are associated with an increase in Pa_{CO_2} from 5.65 to 7.02 kPa; so indicating a dose-related respiratory depressant effect of infusions of Althesin.

The safety of Althesin infusions for the maintenance of anaesthesia is further supported by Böggild-Madsen and Cargnelli (1978), who describe a case report where Althesin 420 mg (total steroid) was accidentally infused over a period of 2 min without any pronounced sequelae. However, a factor limiting the use of continuous infusions of Althesin may be the respiratory depression seen with rates of infusion greater than 2 MIR.

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EFFETS HEMODYNAMIQUES LIES A LA DOSE ADMINISTREE LORS D'INFUSIONS CONTINUES D'ALTHESINE CHEZ L'HOMME

RESUME

Les effets cardiovasculaires des infusions d'althésine administrée à divers taux pour compléter l'anesthésie induite à l'aide de protoxyde d'azote, ont été étudiés sur 7 malades respirant spontanément et sur 11 malades ventilés artificiellement à une Pa_{CO_2} normale. Pendant la respiration spontanée, on a associé les infusions d'althésine à taux croissants aux augmentations de la fréquence cardiaque et du débit cardiaque. La modeste diminution de la pression artérielle (−5%) a été le résultat d'une diminution de la résistance vasculaire. L'infusion d'althésine à des taux croissants a été associée à une augmentation des valeurs de la Pa_{CO_2}. Pendant la ventilation artificielle, l'infusion d'althésine à des taux croissants (jusqu'à huit fois le taux d'infusion minimal) a provoqué en fonction de la dose des diminutions de la pression artérielle et de la résistance vasculaire systémique, alors que la fréquence et le débit cardiaques ont augmenté légèrement à tous les taux d'infusion.

DOSISBEZOGENE HÄMODYNAMISCHE WIRKUNGEN UNUNTERBROCHENER ALTHESININFUSIONEN IM MENSCHEN

ZUSAMMENFASSUNG

Die kardiovaskulären Wirkungen von Althesininfusionen mit verschiedenen Geschwindigkeiten zur Erganzung von Lachgasnarkose wurden in sieben, spontan-atmendenden Patienten und 11, künstlich auf einen normalen Pa_{CO_2} ventilierten Patienten untersucht. Während des spontanen Atmens waren ansteigende Althesininfusionsraten mit ansteigender Pulszahl und Herzminutenvolum verbunden. Der bescheidene Abfall im arteriellen Blutdruck (−5%) ergab sich aus verringertem Gefasswiderstand. Erhöhte Althesininfusionsraten waren mit steigenden Pa_{CO_2}-Werten verbunden. Während kunstlicher Ventilierung verursachten ansteigende Althesininfusionsraten (bis zu achtmal die Mindestinfusionsrate) dosisbezogene Abfälle des arteriellen Blutdrucks und des systemischen Gefasswiderstands, wahrend die Pulszahl und Herzminutenvolum bei allen Infusionsraten leicht erhoht waren.

EFECTOS HEMODINAMICOS RELACIONADOS CON LAS DOSIS EN INFUSIONES CONTINUAS DE ALTESINA EN EL HOMBRE

SUMARIO

Se estudiaron los efectos cardiovasculares de infusiones de Altesina a varios ritmos para suplir la anestesia por óxido nitroso, en siete pacientes que respiraban espontáneamente y en 11 pacientes ventilados artificialmente hasta un Pa_{CO_2} normal. Durante la respiración espontánea, los ritmos crecientes de infusión de Altesina fueron asociados con aumentos en el ritmo y rendimiento cardíacos. El descenso modesto de la tensión arterial (−5%) resultó de una reducción de la resistencia vascular. Ritmos crecientes de infusión de Altesina fueron asociados con valores crecientes de Pa_{CO_2}. Durante la ventilación artificial, los ritmos crecientes de infusión de Altesina (hasta ocho veces el ritmo mínimo de infusión) ocasionaron descensos de tensión arterial y de resistencia vascular sistémica en relación con las dosis, mientras que el ritmo y rendimiento cardíacos aumentaban ligeramente a todos los ritmos de infusión.

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METABOLIC EFFECTS OF INDUCED HYPOTENSION WITH TRIMETAPHAN AND SODIUM NITROPRUSSIDE

J. A. W. WILDSMITH, G. B. DRUMMOND AND W. R. MACRAE

SUMMARY

In two groups of patients undergoing induced hypotension with sodium nitroprusside or trimetaphan blood concentrations of lactate, pyruvate and standard bicarbonate did not differ significantly between the groups. In the nine patients who received trimetaphan there was a progressive, but statistically non-significant, decrease in mean lactate. Nitroprusside (15 patients) was associated with a small increase in mean lactate, but at low dosage there was a small decrease. No relationship to dose rate of nitroprusside was found with these short-term infusions. It is concluded that sodium nitroprusside can be used safely for induced hypotension at doses less than 1.5 mg kg^{-1} and that simple blood-gas analysis is adequate for the assessment of toxic effects when greater doses are given.

Since its introduction for inducing hypotension during anaesthesia (Jones and Cole, 1968) sodium nitroprusside has become widely used because its brief duration of action allows accurate control of hypotension and rapid restoration of arterial pressure at the end of the procedure, although there has always been concern about toxicity because metabolism of sodium nitroprusside results in formation of cyanide. Vesey, Cole and Simpson (1976), having reviewed case reports of presumed cyanide poisoning after nitroprusside and having measured cyanide concentrations in plasma and red blood cells during and after its infusion in man, made recommendations regarding the safe maximum dose. However, cyanide measurements have been questioned as suitable indicators of exposure to cyanide after nitroprusside (Smith and Kruszyna, 1976).

Cyanide blocks oxidative phosphorylation by the cytochromes. Some energy is produced anaerobically by glycolysis with production of lactate when pyruvate cannot enter the Kreb's cycle. We have studied blood lactate and pyruvate concentrations as indicators of this effect of cyanide release in patients receiving nitroprusside to induce hypotension during anaesthesia. Patients who received trimetaphan were studied as controls.

METHODS

Twenty patients undergoing middle ear surgery for which hypotensive anaesthesia was indicated were studied. The nature of the study was explained to the patient and consent obtained. Premedication was with oral diazepam 10 mg. Anaesthesia was induced with thiopentone 250–400 mg and endotracheal intubation performed with the aid of pancuronium 6–8 mg. Anaesthesia was maintained with 50% nitrous oxide in oxygen with halothane 1–2%. The lungs were ventilated artificially at 15 b.p.m. using a Cape–Waine anaesthetic ventilator (Cape Engineering Ltd) with tidal volume set so that expired volume, measured with a Wright respirometer (British Oxygen Company Ltd), equalled that indicated by the Radford (1955) nomogram.

After induction of anaesthesia a 19-gauge Venflon cannula (Everett Medical Products Ltd) was inserted percutaneously into a radial artery to allow measurement of arterial pressure and sampling of arterial blood. After 15 min of stable anaesthesia samples of arterial blood were collected for estimation of lactate, pyruvate and haemoglobin concentrations and for blood-gas analysis. An infusion of 0.9% saline containing either sodium nitroprusside (prepared by the hospital pharmacy) or trimetaphan (Arfonad, Roche) was started. Allocation to either drug was on a random basis and infusion rates were adjusted to produce a systolic arterial pressure of 60 mm Hg. The infusion was continued until the end of surgery, when a second set of samples was taken. Pancuronium was antagonized with neostigmine, the tracheal tube removed, and the patient breathed 35% oxygen from a Ventimask (Vickers Medical Ltd) until a third set of samples was taken 1 h after the second. The arterial cannula was then removed.

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Blood samples for lactate and pyruvate and blood-gas estimation were drawn into two heparinized iced glass syringes. One was sealed and placed in an ice-water mixture for transport to the laboratory where analyses for H^+, Pa_{O_2} and Pa_{CO_2} were performed using an IL 213 microelectrode system. Standard bicarbonate was derived from H^+ and Pa_{CO_2} using the Siggaard-Andersen alignment nomogram. The lactate–pyruvate sample was immediately decanted into an iced glass tube. An aliquot was aspirated to an iced glass pipette, placed in an equal volume of iced perchloric acid, the mixture centrifuged, and the supernatant liquid assayed for lactate and pyruvate using an enzymatic method (The Boehringer Corporation (London) Ltd).

Following the comparative study another six patients who received nitroprusside were studied to provide more data for analysis of the dose–effect relationship on lactate–pyruvate changes.

Differences between the two randomized groups were compared using a *t* test for two means, and changes within groups compared with a paired *t* test.

RESULTS

Table I shows the details of the two groups of patients in the comparative study. Those who received trimetaphan were younger, heavier and underwent procedures of shorter duration than those who received nitroprusside, but none of the differences was statistically significant. The results from one patient in each group were incomplete and have been omitted.

Table II summarizes the blood-gas data. The patients in both groups were well oxygenated and there were minimal changes in mean Pa_{CO_2}.

Table III summarizes the lactate, pyruvate and standard bicarbonate concentrations and the lactate/pyruvate ratios of the 18 patients in the comparative study. Changes in the measurements were generally small and inconsistent. There was a small progressive decrease in mean lactate concentration in those who received trimetaphan whereas there was a small increase in the nitroprusside group between the second and third samples. In none of these measurements were within-group changes or between-group differences statistically significant.

Table III also summarizes the data for the additional six patients studied with nitroprusside infusion. Changes in lactate concentration in all 15 patients receiving nitroprusside were analysed in respect of both total dose and dose rate and no obvious relationships were apparent; neither were changes in lactate concentration related to duration of hypotension.

Lactate concentration decreased in the majority of patients (fig. 1) and the slight increase in mean lactate concentration in the original nitroprusside group was caused almost entirely by one patient whose arterial pressure was resistant to the effect of nitroprusside from the outset. The results for this patient are shown in table IV, with some subsequent blood-gas values and vitamin B_{12} concentrations: the lactate concentration increased and there was a decrease in standard bicarbonate; the lactate/pyruvate ratio decreased and the excess lactate value (Huckabee, 1958) was negative. At the end of the procedure the patient's condition was clinically un-

TABLE I. *Age, sex, weight and duration of surgery in two groups of nine patients who received nitroprusside or trimetaphan. (Mean ± SD)*

	Nitroprusside	Trimetaphan
Age (yr)	36 ± 18	29 ± 10
Sex	5M 4F	6M 3F
Weight (kg)	62 ± 7	65 ± 15
Duration of surgery (min)	62 ± 24	48 ± 29

TABLE II. *Summary of blood-gas data (kPa) (mean ± SD) in the two groups of patients. Samples taken at the start (I) and finish (II) of hypotension, and 1 h after the procedure (III)*

	Nitroprusside		Trimetaphan	
Sample	Pa_{O_2}	Pa_{CO_2}	Pa_{O_2}	Pa_{CO_2}
I (IPPV: FI_{O_2} 0.5)	27 ± 5	5.0 ± 0.6	30 ± 6	5.1 ± 0.7
II (IPPV: FI_{O_2} 0.5)	25 ± 6	5.2 ± 0.7	23 ± 9	5.3 ± 1.2
III (SV: FI_{O_2} 0.35)	19 ± 3	5.6 ± 0.6	17 ± 5	5.3 ± 0.4

TABLE III. *Lactate, pyruvate, lactate/pyruvate ratio and bicarbonate data (means ± SD) of patients studied. Groups* (n = 9) *in comparative study and* (n = 6) *the additional group who received nitroprusside. I = samples at start of procedure, II = samples at end of procedure and III = samples* 1 *h after the procedure. Detailed figures are available from the authors*

Group measurement	Nitroprusside ($n = 9$)	Trimetaphan ($n = 9$)	Nitroprusside ($n = 6$)
Lactate (mmol litre^{-1})			
I	0.85 (0.30)	0.87 (0.22)	1.05 (0.44)
II	0.85 (0.31)	0.83 (0.28)	0.95 (0.32)
III	0.89 (0.61)	0.73 (0.29)	0.80 (0.32)
Pyruvate (mmol litre^{-1})			
I	0.050 (0.019)	0.043 (0.018)	0.064 (0.024)
II	0.053 (0.012)	0.048 (0.014)	0.058 (0.013)
III	0.051 (0.033)	0.042 (0.014)	0.050 (0.014)
Lactate/pyruvate ratio			
I	17.5 (5.9)	25.4 (17.5)	16.8 (5.7)
II	16.3 (4.8)	13.0 (7.3)	16.2 (4.5)
III	18.1 (10.6)	19.3 (9.9)	16.9 (8.1)
Bicarbonate (mmol litre^{-1})			
I	23.2 (2.0)	22.3 (1.4)	21.2 (2.3)
II	22.9 (2.3)	22.4 (1.8)	20.8 (2.6)
III	22.2 (1.5)	21.6 (1.3)	20.8 (1.7)
Dose rate (μg kg^{-1} min^{-1})	12.1 (9.9)	—	12.6 (15)
Total dose (mg kg^{-1})	0.68 (0.5)	—	0.38 (0.3)

remarkable and within 3 h standard bicarbonate had increased spontaneously.

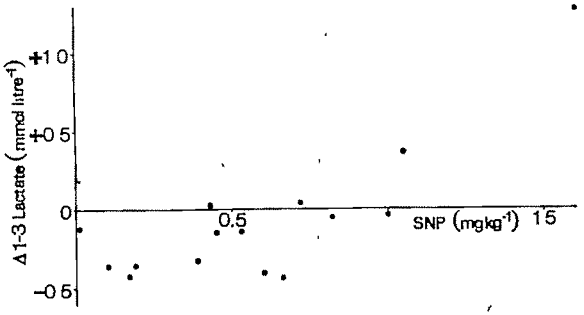

FIG. 1. Relationship between dose of nitroprusside (SNP) and change in lactate concentration between the start of hypotension and 1 h after the operation.

DISCUSSION

Certain physiological and other safeguards are necessary to allow blood lactate concentrations to be used to assess intracellular acidosis. Although it is an indirect method it is the best available (Cohen and Simpson, 1975). Oxygen delivery to the tissues must be adequate: the patients in the present study were all well oxygenated and cardiac output is known to be normal or slightly increased during induced hypotension with nitroprusside (Wildsmith et al., 1973). Changes in $P\text{CO}_2$, particularly hypocapnia, affect lactate concentration (Cohen and Woods, 1976) and for that reason we maintained normocapnia. Infusion of glucose can increase blood lactate (Cohen and Woods, 1976); we gave the drugs in saline. Blood was withdrawn from an arterial cannula to avoid stasis. All glassware was iced and the specimen for lactate decanted into perchloric acid as soon as possible so that the effect of red cell glycolysis after withdrawal was minimal.

Lactate and pyruvate data are often expressed as the ratio of the two, but we do not believe this to be valuable. In the one patient with clear changes, this ratio decreased when it would have been expected to increase. This was because there was a greater proportional increase in pyruvate than in lactate. Excess lactate has also been used to indicate changes in lactate concentration independent of alterations in pyruvate (Huckabee, 1958). Mathematically, however, this figure is not independent of pyruvate (Cohen and Woods, 1976) and in one patient the change was the reverse of that which would be expected.

The results show that hypotensive anaesthesia with trimetaphan is not associated with any evidence of

TABLE IV. *Results from patient* 2: *28-yr old, 54-kg female; non-smoker who received sodium nitroprusside* 86 *mg in* 42 *min.* 1 = *start of hypotension*: 2 = *end of operation*: 3 = 1 *h after procedure*: 4 = 3 *h after procedure*: 5 = 1 *day after procedure*

	Sample no.				
	1	2	3	4	5
Lactate (mmol litre^{-1})	1.12	1.48	2.39	—	—
Pyruvate (mmol litre^{-1})	0.04	0.08	0.13	—	—
Lactate/pyruvate ratio	28.0	18.5	18.4	—	—
Excess lactate (mmol litre^{-1})	—	−0.76	−0.75	—	—
Hydrogen ion (nmol litre^{-1})	34.0	42.0	39.0	41.0	38.0
Pa_{CO_2} (kPa)	5.8	6.5	5.6	4.8	5.3
Bicarbonate (mmol litre^{-1})	25.5	22.0	21.5	22.5	26.0
Pa_{O_2} (kPa)	19.5	26.0	17.9	11.2	13.2
FI_{O_2}	0.5	0.5	0.35	0.21	0.21
B_{12} (ng litre^{-1})	—	—	699.0	—	979.0

cellular hypoxia. Mean lactate concentration decreased slightly with this agent, presumably because peripheral perfusion was improved by vasodilatation. Increased oxygen tension during anaesthesia or simple physical inactivity could also have been responsible, but normotensive halothane anaesthesia produces a slight increase in lactate concentration (Chamberlain and Lis, 1968; Yamazaki et al., 1975). Sodium nitroprusside in low doses also decreased lactate concentrations and it has been used (Taradosh and Jacobsen, 1973) to treat idiopathic lactic acidosis associated with poor peripheral perfusion.

With larger doses, the lactate concentration may increase, presumably as the toxic effect begins to counter the effect on perfusion. The patient who showed resistance to the hypotensive effect of sodium nitroprusside required 1.6 mg kg^{-1} and had the greatest increase in lactate concentration (fig. 1). Although the increase was small and recovery uneventful, this case shows the need to limit total dosage in acute administration, and these results would support the suggested maximum dose of 1.5 mg kg^{-1} based on cyanide studies (Vesey, Cole and Simpson, 1976). Suggestions have also been made regarding the maximum safe dose rate (Editorial, 1978)—a dose of 10 μg kg^{-1} min^{-1} being quoted. While this may apply to administration over a period of days, our results indicate little relationship to dose rate during hypotensive anaesthesia.

The increase in blood lactate concentration in the resistant patient could have been caused by a reduction in hepatic clearance because of a reduction in liver blood flow, rather than by increased production of lactate. Little is known about liver blood flow during administration of nitroprusside, but clearance of indocyanine green has been used as an indicator of this and is not influenced by infusion of nitroprusside during halothane anaesthesia (Abdel Salam et al., 1976).

This study investigated the effects of clinical use of sodium nitroprusside on metabolism. Instead of measuring cyanide concentrations, and attempting to deduce toxicity indirectly, we looked for alteration in the metabolic state. When it is used within its known toxic concentrations, there is no significant metabolic upset. This means that for practical purposes the drug can be administered in normal doses without fear of producing metabolic acidosis, except in patients with known contraindications (Cole, 1978).

Unfortunately, this does not mean that the problem of metabolic acidosis as a potential complication can be ignored. There is no means of predicting how much drug will be needed for any particular patient. Most require only small amounts, but occasionally doses approaching 1.5 mg kg^{-1} are needed. It has been argued that safe use of nitroprusside requires ready access to lactate estimation (Editorial, 1978), but our results confirm animal studies which suggested that changes in lactate are mirrored by changes in bicarbonate concentration (Simpson et al., 1977). Blood-gas analysis is easier, quicker and cheaper to perform and far more readily available. We would consider that this estimation is adequate for assessing toxicity following acute administration during anaesthesia, and make it when the total dose is likely to exceed 1.5 mg kg^{-1}.

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EFFETS METABOLIQUES DE L'HYPOTENSION INDUITE PAR LE TRIMETAPHAN ET LE NITROPRUSSIATE DE SODIUM

RESUME

Sur deux groupes de malades subissant une hypotension induite par le nitroprussiate de sodium ou par le trimétaphan, les concentrations de lactate dans le sang de même que les concentrations de pyruvate et de bicarbonate standard n'ont pas grandement différé dans les deux groupes. Sur neuf malades auxquels on avait administré du trimétaphan, on a constaté une diminution progressive, mais sans grande signification statistique, de la valeur moyenne du lactate. Le nitroprussiate (administré à 15 malades) a été associé à une légère augmentation de la valeur moyenne du lactate, mais à faibles doses, on en a constaté une légère diminution. On n'a trouvé aucune relation dose-taux de nitroprussiate avec ces infusions à court terme. On en a conclu que le nitroprussiate de sodium peut être utilisé en toute sécurité pour induire l'hypotension à des doses inférieures à 1,5 mg kg^{-1} et qu'une simple analyse sang-gaz est adéquate pour évaluer les effets toxiques lorsqu'on administre des doses plus importantes.

STOFFWECHSELWIRKUNGEN KÜNSTLICH HEREEIGEFÜHRTER HYPOTONIE MIT TRIMETAPHAN UND NITROPRUSSIDNATRIUM

ZUSAMMENFASSUNG

In zwei, sich künstlich herbeigefuhrter Hypotonie mit Nitroprussidnatrium oder Trimetaphan unterziehenden Gruppen von Patienten unterschieden sich die Blutkonzentrationen von Laktat, Pyruvat und Standardbicarbonat nicht wesentlich zwischen den beiden Gruppen. In den neun Patienten, die Trimetaphan erhielten, fand ein progressiver, aber statistisch unbedeutender Abfall im mittleren Laktatgehalt statt. Nitroprussid (15 Patienten) war mit einem geringen Anstieg im mittleren Laktatgehalt verbunden, aber bei niedriger Dosierung fand ein geringer Abfall statt. Bei diesen kurzfristigen Infusionen wurde keine Beziehung zur Dosierung von Nitroprussid festgestellt. Es wird der Schluss gezogen, dass Nitroprussidnatrium bei Dosen unter 1,5 mg/kg ohne Gefahr fur künstlich herbeigeführte Hypotonie benutze werden kann, und dass eine einfache Blutgasanalyse fur die Beurteilung schädlicher Wirkungen bei Verwendung grosserer Dosen ausreicht.

EFECTOS METABOLICOS DE LA HIPOTENSION INDUCIDA MEDIANTE TRIMETAFAN Y NITROPRUSIATO DE SODIO

SUMARIO

En dos grupos de pacientes sometidos a hipotensión inducida mediante nitroprusiato de sodio o trimetafán, no difirieron de manera significativa entre los grupos las concentraciones de lactato en la sangre y las concentraciones de piruvato y de bicarbonato normal. En los nueve pacientes a quienes fue administrado trimetafán, hubo una reducción progresiva de lactato medio, aunque no-significativa desde el punto de vista estadístico. Se halló (15 pacientes) nitroprusiato asociado con un ligero aumento de lactato medio, pero en dosajes bajos, se registró una pequeña reducción. No se encontró ninguna relación con el porcentaje de las dosis de nitroprusiato en estas infusiones de corta duración. Se concluye que puede usarse en toda seguridad el nitroprusiato de sodio para hipotensión inducida en dosis menores de 1,5 mg kg^{-1} y que es adecuado un simple análisis sangre-gas para evaluar los efectos tóxicos cuando se administren dosis mayores.

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POSTOPERATIVE SERUM CHOLINESTERASE ACTIVITY FOLLOWING SUCCESSFUL RENAL TRANSPLANTATION

D. W. RYAN

SUMMARY

For 6 months after renal transplant serum cholinesterase concentrations were measured in 10 patients. The value decreased in the first 15 days after operation, but was normal thereafter. Liver function tests were normal throughout the study; the cholinesterase changes were independent of immunosuppressive therapy.

In patients with chronic renal failure the serum cholinesterase concentration may vary, although it is usually in the normal range (Ryan, 1977). Cholinesterase activity has been measured in patients who underwent renal transplant to determine if the value is affected by an improvement in renal function.

PATIENTS AND METHODS

Ten patients receiving regular haemodialysis who underwent renal transplantation were studied. The age range was 11–50 yr, and in all but two the cause of the renal disorder was known (table I). Liver function tests were normal in all patients, and none received a blood transfusion before surgery. Serum cholinesterase concentration, dibucaine number, liver function tests and serum protein concentration were measured before and serially after operation.

Sampling and measurement of serum cholinesterase

Cholinesterase concentration was measured by the method based on benzyl choline hydrolysis (Kalow and Lindsay, 1955). Dibucaine numbers were measured by the method of Kalow and Genest (1957). After surgery blood was sampled between 10 and 15 days in seven patients in hospital. In three patients the sample was obtained at the first return hospital visit. Thereafter blood was sampled at approximately 2-week intervals over the next 3 months, with a final sample at 6 months after the transplant.

Anaesthetic technique

All the patients were anaesthetized using a conventional technique described previously (Ryan, 1977). During the operation blood and other fluids were transfused as appropriate; prednisolone 32 mg and azothioprine 150 mg were also given. (Patient 9 received prednisolone 16 mg and azothioprine 75 mg.)

Management after operation

Each patient received a 60-g protein diet for 15 days and thereafter the diet was unrestricted. In every case rejection episodes occurred, and each patient received treatment between the 3rd and 5th day after operation with methyl prednisolone 1 g. Patient 3 required further treatment for rejection between days 8 and 10.

The patients were discharged from hospital approximately 3 weeks after transplantation, while receiving azothioprine 150 mg and prednisolone 40 mg daily. (Patient 9 received 75 mg and 12 mg respectively.) Fifty days after operation the dose of azothioprine was reduced to 100 mg and that of prednisolone to 35 mg per day. Prednisolone was then reduced at a rate of 5 mg for each month after this date to a final maintenance dose of 10 mg daily.

RESULTS

Nine patients were alive 6 months after transplantation. Patient 4 died 4 months after operation from a myocardial infarction. A wide range of cholinesterase activity was found before operation (0.25–1.45 u. litre^{-1}; mean 0.84 ± 0.34). This finding was comparable to a previous study of patients with chronic renal failure (table II). All dibucaine numbers were normal (table I).

In the initial 15 days after surgery the cholinesterase concentration decreased in many patients, but this was not consistent and in patients 6 and 10 there was an increase (figs 1, 2). The values returned towards normal over the next 15 days; although the mean value was less than the mean before operation ($P < 0.01$), most values were within the normal range. All values were within the normal range thereafter

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TABLE I. *Preoperative details of patients in the study. PK = polycystic kidneys; Hy = hydronephrosis; CGN = chronic glomerulonephritis; FGN = focal glomerulonephritis; HSP = Henoch–Schoenlein purpura; * unknown cause*

						Serum concentrations			
Patient	Age (yr)	Sex	Weight (kg)	Height (m)	Diagnosis	Cholinesterase (0.62–1.37 u. litre^{-1})	Bilirubin (4–20 mg dl^{-1})	Albumin (35–50 g dl^{-1})	Dibucaine number (70–95)
1	43	M	77	1.84	PK	0.76	20	44	80
2	19	F	41	1.59	Hy	0.52	16	23	80
3	50	F	41	1.54	PK	0.94	8	43	76
4	48	M	74	1.70	CGN	1.45	13	38	77
5	49	M	77	1.66	*	1.06	6	40	81
6	26	M	50	1.57	FGN	0.25	15	40	75
7	45	F	54	1.66	*	0.73	8	36	79
8	39	M	76	1.67	CGN	1.03	15	37	79
9	11	F	29	1.27	HSP	1.04	12	36	77
10	45	M	67	1.59	FGN	0.58	10	36	89
Mean	37.5		58.6	1.61		0.83	12.3	37.3	79
SD	±13.8		±17.9	±0.15		±0.34	±4.3	±5.8	±4
Range	11–50		29–77	1.27–1.84		0.25–1.45	6–20	23–44	75–80

TABLE II. *Serum cholinesterase concentrations (u. litre^{-1}) before and after operation in the 10 patients. Comparison with preoperative data in patients with renal failure (Ryan, 1977). Values of P are from Student's t test, comparing each time period with the next; n.s. = not significant; n = no. samples taken*

	Before operation	After transplant (days)						
		0–15	16–30	31–45	46–60	84	184	Ryan (1977)
Mean	0.84	0.54	0.68	0.71	0.75	0.79	0.99	0.87
Range (normal = 0.62–1.37)	0.25–1.45	0.38–0.7	0.52–0.97	0.52–0.88	0.56–0.94	0.61–0.91	0.75–1.27	0.12–3.4
SD	0.34	0.11	0.15	0.13	0.11	0.11	0.15	0.56
SEM	0.11	0.04	0.04	0.04	0.03	0.03	0.05	0.07
n	10	7	10	12	13	11	9	64
P	—	<0.02	<0.04	n.s.	n.s.	n.s.	<0.001	—

for the next 50 days (table II). A sharp increase in cholinesterase concentrations was found between the 84- and 184-day samples ($P<0.001$), but this was not significantly different from the values before operation. Liver function tests were unchanged throughout the period of the study. The protein concentrations were normal before operation, but patient 2 had a low albumin concentration (23 g dl^{-1}) which rapidly returned to normal after operation. The protein and albumin concentrations remained normal after operation.

DISCUSSION

Cholinesterase activity before operation varied considerably between the 10 patients, who all had normal dibucaine numbers. After operation changes occurred which were often marked, but the trend, although downwards, was unpredictable in the individual. Cholinesterase activity returned to normal in about 30 days followed by a plateau effect with a sudden increase at 184 days.

Decreases in cholinesterase activity in surgical patients have been reported by Burnett and Cohen (1955) and also Zarday and others (1975) in renal transplant patients following operation. Zarday's group (1975) suggested that the decrease may have been caused by prednisolone, possibly by inhibiting glucocorticoid or protein synthesis in the liver, but azothioprine may also depress liver function (Zarday et al., 1972). However, liver function and protein synthesis remained normal in all 10 of our patients who received both prednisolone and azothioprine.

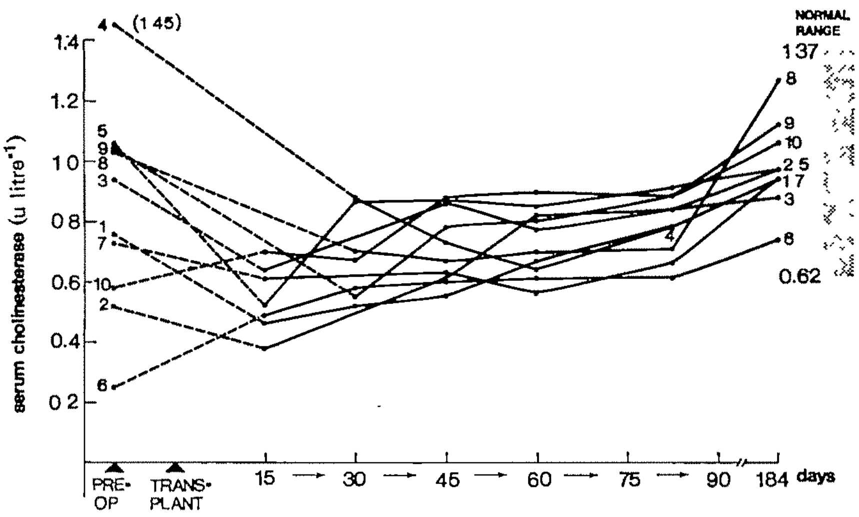

FIG. 1. Comparison of individual serum cholinesterase values during the study.

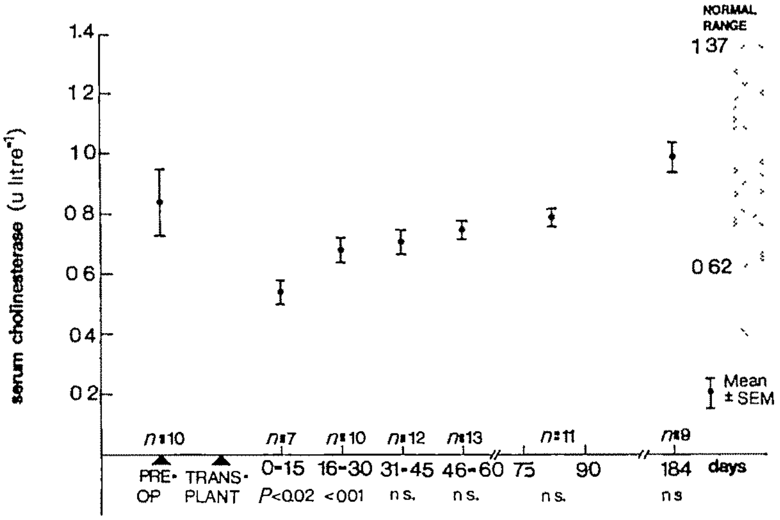

FIG. 2. Mean cholinesterase concentrations before and after renal transplantation. Values obtained before and after operation were compared using Student's t test: n.s. = not significant.

The liver is the site of cholinesterase production and improvement or decline in liver function is sensitively mirrored by serum cholinesterase changes whilst the patient is receiving full immunosuppressive treatment (Evans and Lehman, 1971). It can be concluded that the changes in cholinesterase in this study are unrelated to liver function and reflect extracellular fluid compartment changes.

The serum cholinesterase is not a sensitive guide to renal function, unlike liver function; the changes seen in this study occurred whilst a steady improvement in transplanted kidney function occurred. It is noteworthy that immunosuppressive therapy does not impair cholinesterase synthesis by the liver. The return to normal renal function is mirrored by a change in the range of values seen in haemodialysis patients to a more normal distribution.

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ACTIVITE CHOLINESTERASE POSTOPERATOIRE DANS LE SERUM APRES UNE GREFFE DE REIN COURONNEE DE SUCCES

RESUME

On a mesuré sur 10 malades, et ce pendant les 6 mois qui ont suivi une greffe de rein, les concentrations de cholinestérase dans le sérum. Leurs valeurs ont diminué pendant les 15 premiers jours qui ont suivi l'opération, mais elles sont redevenues normales après cela. Les essais de la fonction hépatique ont été normaux pendant toute la durée de l'étude; les variations de la cholinestérase ont été indépendantes de la thérapie immunosuppressive.

POSTOPERATIVE SERUMCHOLINESTERASE-TÄTIGKEIT NACH ERFOLGREICHER NIERENTRANSPLANTATION

ZUSAMMENFASSUNG

Nach Nierentransplantation wurden 6 Monate lang in 10 Patienten die Serumcholinesterasekonzentrationen gemessen. In den ersten 15 Tagen nach der Operation fiel der Wert, war aber danach normal. Die Leberfunktionsprufungen ergaben wahrend der ganzen Untersuchung normale Resultate; die Cholinesteraseveränderungen waren unabhängig von immunkörperunterdruckender Therapie.

ACTIVIDAD POSTOPERATORIA DE LA COLINESTERASA EN EL SUERO TRAS UN TRANSPLANTE RENAL EXITOSO

SUMARIO

Se midieron las concentraciones de colinesterasa en el suero de 10 pacientes al cabo de 6 meses de someterse a transplante renal. El valor disminuyó durante los primeros 15 días después de la operación, pero posteriormente se normalizó. Las pruebas de funcionamiento del hígado resultaron normales a través del estudio; los cambios en la colinesterasa dependieron de la terapia inmunosupresiva.

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GLYCOPYRROLATE AS A PREMEDICANT: COMPARISON WITH ATROPINE

T. D. McCubbin, J. H. Brown, K. M. S. Dewar, C. J. Jones and A. A. Spence

SUMMARY

A double-blind comparison of glycopyrrolate with atropine as the anticholinergic component of premedication was made in 200 patients undergoing minor or intermediate surgical procedures. Glycopyrrolate was associated with a smaller increase in heart rate, but there was no difference between the drugs in respect of cardiac arrhythmia, change in arterial pressure, control of secretions in the upper respiratory tract, frequency of nausea and vomiting after operation or subjective well-being of the patients.

In 1960, glycopyrrolate, a quaternary ammonium compound, was introduced as a potent long-acting anticholinergic agent which apparently offered a smaller frequency of side-effects such as dryness of the mouth, blurring of vision and excessive tachycardia seen with atropine.

More recently, several studies of the relative effects of glycopyrrolate and atropine combined with neostigmine and given i.v. for antagonism of neuromuscular blockade concluded that the glycopyrrolate–neostigmine combination produced a more stable heart rate with a reduced frequency of tachycardia and arrhythmia (Ramamurthy, Ylagan and Winnie, 1971; Klingenmaier et al., 1972; Ramamurthy, Shaker and Winnie, 1972; Mirakhur, Dundee and Clarke, 1977). Being a quaternary ammonium compound, glycopyrrolate crosses the blood–brain barrier to a minimal degree compared with atropine, a tertiary amine (Proakis and Harris, 1978). Therefore, glycopyrrolate should exert none of the central effects that occasionally occur with atropine. Wyant and Kao (1974) found that glycopyrrolate was a more effective antisialogogue than atropine. Glycopyrrolate is at present freely available in the U.S.A. and is being widely promoted on the basis of the attributes mentioned above.

We have undertaken a double-blind comparison of atropine with glycopyrrolate as the anticholinergic components of premedication, to determine if the latter drug appeared to have any advantages over atropine.

PATIENTS AND METHODS

Two hundred healthy patients were studied; none was receiving concurrent drug therapy. The age and sex distribution and types of operation are shown in table I. Premedication consisted of morphine 10 mg and either atropine 0.6 mg or glycopyrrolate 0.2 mg (randomly allocated) administered i.m. approximately 1 h before operation. Just before the injection, the heart rate and arterial pressure were recorded (resting values).

TABLE I. *Patient distribution, sex, age and operation; "miscellaneous" includes circumcision and excision of minor lumps*

	Atropine	Glycopyrrolate
n	100	100
Male	56	63
Female	44	37
Age (yr) mean	46.4	45.4
range	14–85	15–87
Operation		
Hernia/testis	31	26
Breast	18	24
Varicose veins	13	14
Haemorrhoids	15	23
Miscellaneous	23	13

Before induction of anaesthesia, the patients were asked:

Do you feel drowsy?
How do you feel otherwise?

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How does your mouth feel—normal, dry or uncomfortably dry?

Anaesthesia was induced with thiopentone 2.5% sufficient to abolish the eyelash reflex, and tracheal intubation was facilitated by suxamethonium 50 mg. Anaesthesia was maintained with 66% nitrous oxide in oxygen supplemented by halothane as necessary using a Magill breathing system. After recovery from suxamethonium the patients breathed spontaneously. E.c.g. was monitored throughout (Memory Monitor, SEM 432, S.E. Labs) and heart rate, arterial systolic pressure (oscillotonometer), and the presence of arrhythmia were recorded before induction, before and following incision, and at 15-min intervals thereafter. At the end of the operation, the oropharynx was aspirated before removal of the tracheal tube and the aspirate volume was judged by the anaesthetist to be "acceptable" or "excessive". Following recovery from anaesthesia, the patients were questioned about the state of the mouth on wakening and about any experience of nausea or vomiting. Patients anaesthetized in the morning were interviewed in the evening of the same day. Patients anaesthetized in the afternoon were interviewed in the morning of the following day. All the anaesthetics were given by a Consultant or Senior Registrar (one of the authors).

Patients were selected from each group and matched for age, sex, type of operation and premedication–induction interval; 67 pairs (134 patients) fulfilled these criteria.

The data were analysed using Chi square test and Student's *t* test for analysis of paired data.

RESULTS

Assessment before induction

Forty per cent of patients in the atropine group and 38% in the glycopyrrolate group felt drowsy; 15% in the atropine group and 16% in the glycopyrrolate group commented spontaneously about mouth dryness; the responses to direct questioning regarding mouth dryness are in table II. There were no significant differences between the drugs in respect of any of these criteria.

TABLE II. *Assessment of dryness of mouth (A) before induction and (B) after operation*

		Atropine	Glycopyrrolate
Uncomfortably dry	A	14	23
	B	46	58
Dry	A	79	71
	B	39	33
Normal	A	7	6
	B	15	9

Observations during operation

Heart rate. Figure 1 shows the percentage of patients in whom there was an increase in heart rate. The only significant difference between the drug groups was in the period before induction, when a significantly higher proportion of patients in the atropine group exhibited an increase in heart rate of $\geqslant 10\%$ ($P<0.05$), $\geqslant 20\%$ ($P<0.01$) and $\geqslant 30\%$ ($P<0.005$).

Table III (matched comparison) shows the mean percentage increase in heart rate attributable to atropine or glycopyrrolate. The only significant difference between the groups was at the period before induction.

TABLE III. *Analysis of matched pairs. Mean % increase in heart rate attributable to atropine or glycopyrrolate*

	Before induction	Before incision	After incision (min)		
			0	15	30
Mean diff.	10.15	5.35	4.42	7.18	6.70
t	3.25	1.30	1.13	1.63	0.84
Deg. freedom	66	66	65	51	13
P	0.005	n.s.	n.s	n.s.	n.s.

Arrhythmia was observed in 10 patients in the atropine group and in 11 in the glycopyrrolate group; eight and six respectively had unifocal or multifocal ventricular ectopic beats or bigeminy. In the glycopyrrolate group, four others developed a heart rate less than 50 beat min^{-1} and one patient had a "wandering pacemaker". In the atropine group, one patient had supraventricular tachycardia and another developed multifocal extrasystoles proceeding to ventricular tachycardia; anaesthesia and operation were discontinued but the patient made an uneventful recovery. No obvious predisposing factors could be found for these arrhythmias. A few patients exhibited decreases in heart rate, but there was no significant difference between the groups.

Arterial pressure. Figure 2 shows the percentage of patients exhibiting increases in arterial systolic pressure equal to or greater than 20 mm Hg and 40 mm Hg compared with the resting value. The majority of patients exhibited a progressive decrease in pressure and there was no significant difference between the two groups (fig. 3).

Secretions. Acceptable control of oropharyngeal secretions was achieved in 94% of patients in the

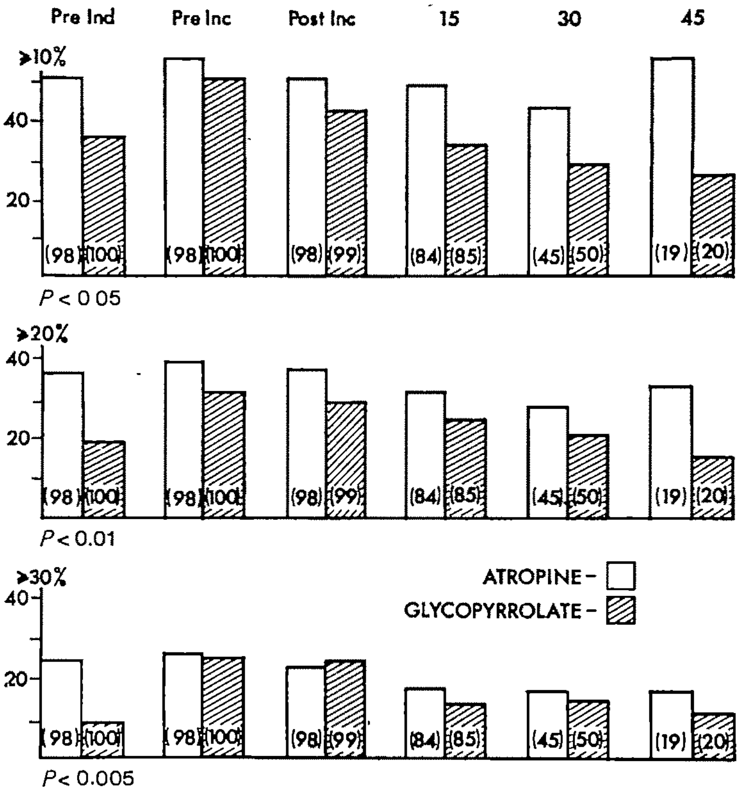

FIG. 1. Percentage of patients exhibiting increases in heart rate ≥10% (upper trace), ≥20% (middle trace) and ≥30% (lower trace), compared with resting value at the times (min) indicated. The number of patients for whom a measurement was available is given in brackets. Pre Ind = before induction; Inc = incision.

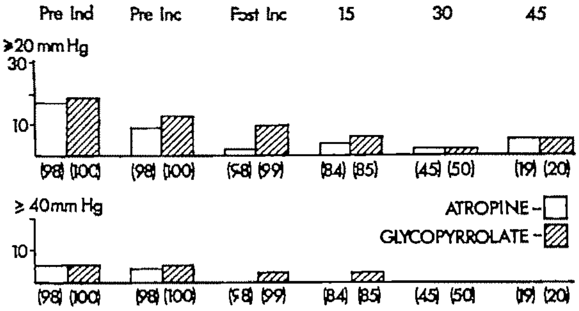

FIG. 2. Percentage of patients exhibiting increases in systolic arterial pressure ≥20 mm Hg (upper trace) and ≥40 mm Hg (lower trace), compared with resting value at the times indicated.

atropine group and in 93% in the glycopyrrolate group.

Assessment after operation. Thirty-eight per cent of patients in the atropine group and 39% in the glycopyrrolate group experienced nausea or vomiting, or both, in the period after operation. The patients' comments as to the state of the mouth on wakening are in table II. Both before and after operation, the majority of patients in both groups complained of mouth dryness, with more in the glycopyrrolate group stating that this was uncomfortable. However, the difference between the groups was not statistically significant.

DISCUSSION

We found that only in the period before induction of anaesthesia did significantly fewer patients in the glycopyrrolate group exhibit increases in heart rate compared with the atropine group. However, that is perhaps the most valid period for direct comparison of the drugs, as subsequent measurements were obviously influenced by a variety of factors associated with anaesthesia and operation. This conclusion is based on analysis of group means and is supported further by the analysis of matched pairs, the latter

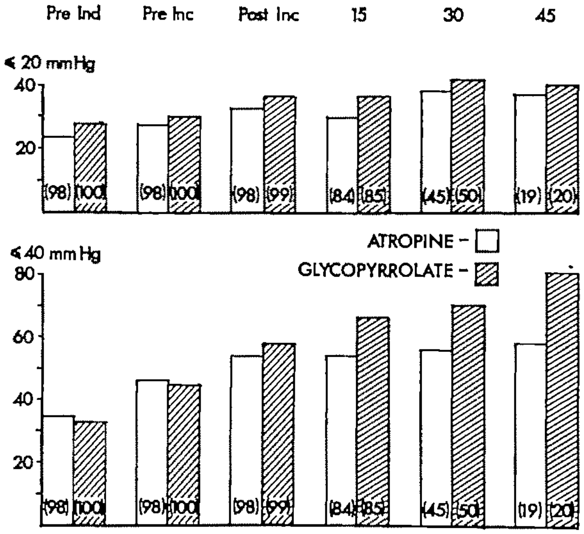

FIG. 3. Percentage of patients exhibiting decreases in systolic arterial pressure ≤20 mm Hg (upper trace) and ≤40 mm Hg (lower trace), compared with resting value at the times indicated.

device being used to reduce the influence of age, sex and operation. A comparison of percentage changes in heart rate between the groups at subsequent periods of measurement failed to reveal any significant differences, although in general a smaller proportion of patients receiving glycopyrrolate showed increases in heart rate during each period of observation compared with those receiving atropine.

Various authors have described improved cardiovascular stability with a reduced frequency of tachycardia and arrhythmia when glycopyrrolate was substituted for atropine in combination with neostigmine to antagonize neuromuscular blockade (Ramamurthy, Ylagan and Winnie, 1971; Klingenmaier et al., 1972; Ramamurthy, Shaker and Winnie, 1972; Oduro, 1975; Mirakhur, Dundee and Clarke, 1977).

The patients in this study were healthy, undergoing relatively simple surgical procedures, and an increased heart rate may be considered acceptable. However, glycopyrrolate may offer advantages in the management of patients with cardiovascular disease or hyperthyroidism, or if a technique for induced hypotension is used. In this study, the majority of arrhythmias were benign and required no treatment; indeed, cardiac arrhythmia is not infrequent with the technique of anaesthesia employed in this investigation (Katz and Bigger, 1970). Mirakhur and others (1978b) noted a reduced frequency of arrhythmia with the use of glycopyrrolate when used as a premedicant, but our findings fail to confirm this.

It has been suggested (Ramamurthy, Ylagan and Winnie, 1971; Ramamurthy, Shaker and Winnie, 1972) that atropine, a tertiary amine, can cross the blood–brain barrier and may cause c.n.s. excitation; glycopyrrolate, a quaternary ammonium compound, cannot readily cross the blood–brain barrier. However, we detected no difference in drowsiness before operation between the two groups.

There was no difference between the groups in the occurrence of nausea and vomiting after operation; the use of morphine in sedation before surgery may account for the high overall frequency of postoperative nausea and vomiting which we noted (Riding, 1960). Dr Riding also demonstrated the antiemetic properties of atropine. It has been observed that the awake patient who has received glycopyrrolate complains less of mouth dryness than does the patient who has received atropine (Ramamurthy, Ylagan and Winnie, 1971). However, our study failed to confirm this either before or after operation.

The routine use of anticholinergic drugs before operation is controversial, but in a recent survey, Mirakhur and others (1978a) pointed out that more than 60% of anaesthetists in the U.K. employ such a drug, and therefore the majority of patients undergoing general anaesthesia receive an anticholinergic agent. We can conclude from this study that glycopyrrolate is an acceptable alternative to atropine, although, apart from considerations of heart rate, it does not have any dramatic advantage over atropine.

ACKNOWLEDGEMENTS

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LE GLYCOPYRROLATE EN TANT QUE PREMEDICATION: COMPARAISON AVEC L'ATROPINE

RESUME

On a fait sur 200 malades devant subir des interventions chirurgicales mineures ou intermédiaires des comparaisons á double inconnue du glycopyrrolate et de l'atropine en tant que composant antichclinergique de la prémédication. Le glycopyrrolate a été associé à une plus petite augmentation de la fréquence cardiaque, mais il n'y a eu aucune différence entre les médicaments en ce qui concerne l'arythmie cardiaque, les variations dans la pression artérielle, le contrôle des sécrétions dans les voies respiratoires supérieures, la fréquence des nausées et des vomissements après l'operation ou le bien-être subjectif des patients.

GLYCOPYRRONIUM-BROMID FÜR DIE VORBEHANDLUNG: VERGLEICH MIT ATROPIN

ZUSAMMENFASSUNG

Ein Doppelblindvergleich zwischen Glycopyrronium-bromid und Atropin als anticholinergischer Teil der Vorbehandlung wurde bei 200 Patienten angestellt, die kleinen oder Übergangsoperationen unterzogen wurden. Glycopyrroniumbromid rief einen kleineren Anstieg der Herztatigkeit hervor, doch gab es keine Unterschiede zwischen den beiden Drogen im Bezug auf kardiale Arrythmie, Änderungen des arteriellen Druckes, Sekretkontrolle im oberen Atmungstrakt, Häufigkeit von Übelkeit und Erbrechen nach der Operation oder das subjektive Wohlbefinden der Patienten.

GLICOPIRROLATO COMO SUSTANCIA DE PREMEDICACIÓN: COMPARACION CON ATROPINA

SUMARIO

Se llevó a cabo en 200 pacientes sometidos a operaciones quirúrgicas menores o intermedias una comparación doble-ciega de glicopirrolato con atropina, como componente anti-colinérgico de premedicación. Se comprobó que el glicopirrolato se acompañaba de un pequeño aumento del ritmo cardíaco, pero que no había diferenciá entre las drogas con respecto a arritmia cardíaca, cambios en la presión arterial, control de secreciones en vías respiratorias altas, frecuencia de las náuseas y vómitos después de la operación o bienestar subjectivo de los pacientes.

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PREVENTION OF DIAZEPAM-INDUCED THROMBOPHLEBITIS WITH CREMOPHOR AS A SOLVENT

M. A. K. MATTILA, M. RUOPPI, M. KORHONEN, H. M. LARNI, L. VALTONEN AND H. HEIKKINEN

SUMMARY

In 104 patients undergoing anaesthesia of short duration, two different solvents, propylene glycol and cremophor, were compared in a double-blind trial. Diazepam 10 mg in a coded solution was injected into a superficial vein of the hand using a small-gauge needle. The vein was examined after 14 days. The frequency of thrombophlebitis with propylene glycol was 62.2% and with cremophor 3.4% ($P < 0.001$). The frequency of pain on injection was also in favour of the new solvent ($P < 0.001$). The possibility of anaphylactic reactions accredited to cremophor, however, restricts the use of the new injection.

Many agents given i.v. can cause irritation of the vein and thrombophlebitis. This type of post-injection thrombophlebitis has generally been considered as a harmless complication, but it can be painful and disabling to the patient, with persisting symptoms.

I.v. diazepam is widely used in anaesthesia and in other fields of medicine for its tranquillizing, anticonvulsant, muscle relaxant and amnesic properties and as an adjuvant to anaesthesia.

In recent years attention has been drawn to thrombophlebitis associated with i.v. diazepam (Coover, 1973; Davis and Keller, 1973; Friedenberg and Barker, 1973; Langdon, 1973; Langdon, Harlan and Bailey, 1973; von Dardel, Mebius and Mossberg, 1976; Hegarty and Dundee, 1977; Graham, Pagano and Conner, 1978). A surprisingly small number of controlled studies are available and there are great variations in the reported frequency of thrombophlebitis (Greenblatt and Koch-Weser, 1973; Langdon, Harlan and Bailey, 1973; Siebke, Ellertsen and Lind, 1976; Hegarty and Dundee, 1977).

Different methods have been described to reduce the frequency of thrombophlebitis (von Dardel, Mebius and Mossberg, 1976; Korttila, Sothman and Andersson, 1976).

We have studied the frequency and clinical importance of post-injection thrombophlebitis by a double-blind technique with two different solvents for diazepam (propylene glycol and cremophor).

PATIENTS AND METHODS

One hundred and four patients (mean age 25.8, range 14–44 yr) undergoing legal abortion or diagnostic curettage were studied. Informed consent was obtained. Immediately before induction of anaesthesia, diazepam 10 mg (Stesolid, Dumex) in a coded solution was given i.v. This solution included either propylene glycol (conventional solvent) or cremophor (new solvent). A 23-gauge disposable needle and 2-ml plastic syringe were used. The injection was administered directly to the largest and straightest superficial dorsal vein of the right hand.

I.v. anaesthesia was administered to the left hand vein by using a Intranule 1.6-mm cannula. The patients received either propanidid (Propantan) or methohexitone (Brietal Sodium) i.v. All other i.v. drugs were administered to the left hand vein.

A post-injection examination was made after 14 days either by one of two anaesthetists or by a trained anaesthesia nurse. The following were noted: swelling, erythema and phlebitis at the vein of either hand. The patients were asked about symptoms. Additionally, the ease of injection of the solution (classified as "good", "fair" or "poor") was studied in a total of 179 patients.

The χ^2 test was used for statistical analysis of the results.

RESULTS

The frequency of thrombophlebitis is shown in table I. Following cremophor there were fewer

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TABLE I. *Frequency (%) of thrombophlebitis after i.v. diazepam dissolved in propylene glycol or cremophor*

Complication	Propylene glycol (right hand)	Cremophor (right hand)	Other anaesthetic agents (left hand)
Swelling			
None	80.0	93.3	95.2
Moderate	20.0{ 8.9	6.7{ 6.7	4.8{ 3.8
Marked	11.1	0	1.0
Erythema			
None	86.7	98.3	96.1
Moderate	13.3{ 8.9	1.7{ 1.7	3.9{ 2.9
Marked	4.4	0	1.0
Phlebitis			
None	37.8	96.6	91.3
Moderate	62.2{ 17.8	3.4{ 1.7	8.7{ 6.7
Marked	44.4	1.7	2.0

instances of swelling ($P < 0.005$) and phlebitis ($P < 0.001$). The difference in the frequency of erythema was not (but almost) significant ($P < 0.05$).

Symptoms such as pain at the site of injection or in the vein, and functional disturbances (table II) were reported by 65.9% of the patients who received diazepam with the conventional solvent and 8.5% of those who received the new solvent ($P < 0.001$).

TABLE II. *Symptoms after i.v. injection of diazepam dissolved in propylene glycol or cremophor* (%)

Pain or functional disturbance	Propylene glycol (right hand)	Cremophor (right hand)	Other anaesthetic agents (left hand)
None	34.1	91.5	91.4
Moderate	65.9{ 34.1	8.5{ 6.8	8.6{ 4.8
Severe	31.8	1.7	3.8

The evaluation of ease of injection is in table III. Diazepam in cremophor was superior ($P < 0.001$).

TABLE III. *Ease of injection of diazepam dissolved in propylene glycol or cremophor* (%)

Solvent	*n*	Good	Fair	Poor
Propylene glycol	82	35.4	37.8	26.8
Cremophor	97	62.9	32.0	5.1

DISCUSSION

There are variations in the reported frequency of post-injection thrombophlebitis (Greenblatt and Koch-Weser, 1973; Langdon, Harlan and Bailey, 1973; Siebke, Ellertsen and Lind, 1976; Graham, Pagano and Conner, 1978). In our study the frequency of thrombophlebitis with propylene glycol was surprisingly high (62.2%) when compared with 0–29% reported previously (Greenblatt and Koch-Weser, 1973; Langdon, Harlan and Bailey, 1973). A possible explanation is that symptoms of thrombophlebitis do not usually appear until after the patient has left hospital. This was seen in a preliminary investigation, in which the same methods were used as in the present study, but where the patient was examined after only 4–6 days. Thus the symptoms and signs of thrombophlebitis reach a maximum between 1 and 2 weeks after injection; at 14 days they are diminishing.

To eliminate all possible physical factors influencing thrombophlebitis, a small-gauge needle was chosen and the injection was given slowly by allowing blood to flow past the needle to dilute and neutralize the injected solutions (Lepoivre and Alderweireldt, 1973). The possible effect of other i.v. drugs was eliminated by injecting them to the other hand, which served as control. In the present study the only variable was the diazepam solvent.

Our results favour cremophor as the frequency of thrombophlebitis was reduced from 62.2% to 3.4%. The advantages of the new solvent are clearly reflected in the patients' symptoms. A decrease in symptoms from 65.9% to 8.5% is an indication of important progress in the comfort and well-being of the patient. Although superficial post-injection thrombophlebitis rarely causes serious complications (Schneider and Mace, 1974), there may be local pain reaction with erythema and swelling and, in some cases, temporary disturbances in function. The routine use of cremophor as a solvent would greatly reduce the discomfort of injection and the potential hazards of venous sequelae.

Von Dardel, Mebius and Mossberg (1976) dissolved an active diazepam substance in soybean oil and emulsified it in water. With diazepam as an emulsion they observed only a 1.1% frequency of thrombophlebitis with a follow-up period of 8.7 days (average). Graham, Pagano and Conner (1978) diluted diazepam in propylene glycol with crystalloid infusion fluid. One day after the injection they observed a 3% frequency of thrombophlebitis in the group which had received diazepam diluted, compared with 16% in patients who had received undiluted diazepam.

Cremophor is also used as a solvent for propanidid and Althesin. Anaphylactic reactions, some being lethal, have been reported with these agents and attributed to cremophor (Doenicke et al., 1973; Clarke et al., 1975; Dundee, 1976). There are reports of anaphylactic reactions with diazepam and cremophor, but there are no data available on the likely frequency (Christensen and Hansen, 1977).

We have found that diazepam dissolved in propylene glycol often caused sticking of the disposable plastic syringes. If the drug was allowed to remain in the syringe, even for a short time, this problem was more likely. With the new solvent ease of injection was significantly improved ($P<0.001$).

In conclusion, we found that diazepam dissolved in cremophor caused significantly less post-injection thrombophlebitis. On the other hand, the possibility of anaphylactic reactions should not be underestimated. The use of diazepam in cremophor should be restricted to circumstances where an anaphylactic shock can be treated effectively.

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PREVENTION PAR LE CREMOPHOR UTILISE COMME SOLVANT DE LA THROMBO-PHLEBITE PROVOQUEE PAR LE DIAZEPAM

RESUME

On a comparé au cours d'une étude à double inconnue deux solvants différents, le propylène-glycol et le crémophor, sur 104 malades subissant une anesthésie de courte durée. On a injecté 10 mg de diazépam dans une solution codée, dans une veine superficielle de la main à l'aide d'une aiguille fine. On a examiné cette veine 14 jours plus tard et on a trouvé que la fréquence de thrombo-phlébite était de 62,2% avec le propylène-glycol et de 3,4% avec le crémophor ($P<0,001$). La fréquence de la douleur après l'injection a aussi été en faveur du nouveau solvant ($P<0,001$). La possibilité de réactions anaphylactiques que l'on associe généralement au crémophor limite cependant l'usage de la nouvelle injection.

VERHINDERUNG VON DURCH DIAZEPAM HERBEIGEFÜHRTER THROMBOPHLEBITIS MIT CREMOPHOR ALS LÖSEMITTEL

ZUSAMMENFASSUNG

Bei 104, sich kurzfristiger Narkose unterziehenden Patienten wurden zwei verschiedene Lösemittel, Propylenglykol und Cremophor, in einem doppelblinden Versuch miteinander verglichen. 10 mg Diazepam in einer codierten Losung wurden in eine Oberflachenvene in der Hand injiziert unter Verwendung einer Nadel von geringem Durchmesser. Die Vene wurde nach 14 Tagen untersucht. Das Vorkommen von Thrombophlebitis betrug mit Propylenglykol 62,2% und mit Cremophor 3,4% ($P<0,001$). Das Auftreten von Schmerzen bei Injektionsstörungen begünstigte ebenfalls das neue Lösemittel ($P<0,001$). Die Cremophor zugeschriebene Möglichkeit von anaphylaktischen Reaktionen schränkt jedoch den Einsatz der neuen Injektion ein.

PREVENCION DE LA TROMBOFLEBITIS INDUCIDA POR DIAZEPAM MEDIANTE EL CREMOFOR COMO SOLVENTE

SUMARIO

En una prueba doble-ciega, se compararon dos solventes distintos, el glicol de propileno y el cremofor, en 104 pacientes sometidos a anestesia de corta duración. Se inyectó en una vena superficial de la mano 10 mg de diazepam en una solución codificada, utilizándose una aguja de pequeño calibre. Después de 14 días, se examinó la veno. La frecuencia de la tromboflebitis con glicol de propileno era de 62,2% y con el cremofor de 3,4% ($P < 0{,}001$). La frecuencia del dolor tras la inyección también milita a favor del nuevo solvente ($P < 0{,}001$). Sin embargo, restringe el uso de lo nueva inyección la posibilidad de reacciones anafilácticas al cremofor.

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EFFECT OF DIFFERENT FLOW PATTERNS ON THE WRIGHT RESPIROMETER

J. A. BUSHMAN

SUMMARY

The problems of using the Wright respirometer for measurements at small rates of flow associated with small volumes are discussed. Accuracy is very dependent on the wave form of the flow passing through it.

The fact that there are problems in measuring low flows with the Wright respirometer has been known for some time and this characteristic of the instrument was clearly defined by Nunn and Ezi-Ashi (1962). They studied continuous flow and showed that with less than 16 litre min^{-1} the registered volume underestimated the absolute volume by an amount which increased very rapidly as flow was reduced.

This report shows that the flow pattern of a given volume passing through the instrument in unit time has a large effect on the volume registered. The flow patterns used, similar to those found in clinical practice, were demonstrated artificially in a way which ensured accurately repeatable results.

MATERIALS AND METHODS

Five different types of Wright respirometer (A to E) were examined, all, apart from one, available on the market. The manufacturers are not named as the history of each instrument before test varied and no conclusions can be made about the relative merits of the instruments from these results.

Test 1

The flow rate required just to maintain rotation of the vane was measured. To take account of the weight of the hands, flow rates were recorded only after the most directly geared hand had rotated by 360°. This "starting flow" was measured by passing an air flow generated by a variable speed fan through a flowmeter (calibrated for air at 20 °C between 0.6 and 5 litre min^{-1} with an accuracy of 1% of full range = 0.05 litre min^{-1}), the respirometer being connected to the flowmeter outlet. Some of the respirometers were affected by the angle of their main axis to the perpendicular.

All instruments A to E were tested, although E was a prototype.

For the first reading each instrument was attached to the rotameter with its axis vertical and the dial horizontal face upwards. The flow rate was then increased smoothly and slowly until the vane could be seen rotating and then decreased until the vane just remained rotating without stalling for 1 min. The test was repeated with the instrument axis horizontal (the face in a vertical plane).

Test 2

Instruments A to D were tested on a rig consisting of a Starling pump ventilating a 5-gallon drum. The respirometers were placed in the circuit, two at a time, in series, at the junction of the Y-piece from the pump with the drum. In each set of measurements the dial on one instrument was vertical and the other horizontal. One instrument was positioned to measure "inspiration", the other expiration. For each procedure the two instruments were changed round so that readings were obtained for each of two positions (vertical and horizontal) and for each direction of flow (inspiration and expiration).

The Starling pump and drum were chosen as a test rig as the combination produces an approximately sinusoidal input from the pump and a high initial flow rate on expiration from the drum because of its compliance and the valve arrangement on the Starling pump.

Figure 1, which shows the difference in flow patterns, was produced using a Fleisch flow transducer and a Greer defocusing manometer. A potentiometric-type recorder with a comparatively low slew

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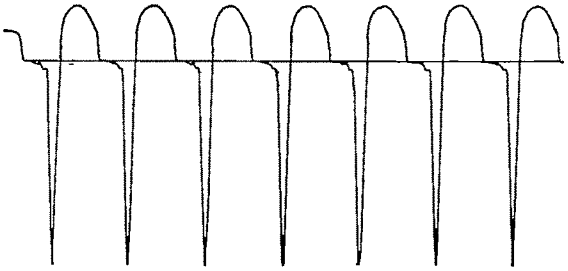

FIG. 1. The "inspiratory" and "expiratory" flow patterns of the Starling pump and drum system. Note the slow sinusoidal shape of the inspiratory flow (upwards) and the fast initial component of the expiratory flow (downwards). The movement of the paper under the pen was from left to right. The magnitude of the fast rising component is an underestimate of the real flow because of the comparatively slow response of the potentiometric recorder used. The pump was set at 200 ml at 12.5 rev min^{-1} for this recording, but the wave form was exactly the same at the high and low settings of the pump, 300 and 100 ml respectively.

rate was used and this underestimates the fast rising component of the expiratory flow.

The actual flows (table I) were measured by displaying the output from the Greer manometer on an oscilloscope screen. This shows a three- to four-fold difference between the inspiratory and expiratory flow rates, a condition sometimes found in clinical practice.

TABLE I. *Peak inspiratory and expiratory flow rates at different volume settings of the Starling pump*

Volume set (ml)	Peak inspiratory flow rate (litre min^{-1})	Peak expiratory flow rate (litre min^{-1})
300	8	25
200	5	18
100	3	11

The stroke volume of the Starling pump was set in turn at one of three volumes—300 ml, 200 ml or 100 ml. The drive belt was adjusted to give 12.5 strokes per min and each test was run for 2 min, the crank of the pump being started and stopped from exactly the same position after 25 complete revolutions.

The respirometers were always started from zero. Each test was performed twice. There was no particular reason for choosing the combination of the respirometers (A with C and B with D) other than each of the pair in any given test was of different manufacture and had a different arrangement of hands on the dial.

The two readings given in table II demonstrate the difference in the flow required to keep the vane rotating when the more or most sensitive hand of the instrument was being rotated upwards compared with when it was running downwards assisted by its own weight.

TABLE II. *Minimum flow required just to keep the vans of each of the five respirometers rotating. The two readings given with the axis horizontal demonstrate the different flows required to move the more or most sensitive hand against or with the aid of gravity*

	Minimal running flows (litre min^{-1})	
Respirometer	Axis vertical	Axis horizontal
A	2.1	2.0/2.2
B	2.25	1.4/2.8
C	1.9	1.1/2.2
D	2.0	2.0/2.0
E	1.76	1.6/1.7

RESULTS AND DISCUSSION

Table II shows the minimum flows for the five respirometers tested. These are similar when the axis of the vane is vertical and the face of the dial is horizontal and uppermost. With the dial face vertical the minimum flow to rotate the vanes changes according to the position of the hands on the dial (two figures under the second heading).

Instrument D had the most highly geared hand (× 10) while the most sensitive hand in it was small. As might be expected, this instrument was not sensitive to its position, although it was difficult to read from a distance with accuracy.

Instrument B was easy to read several feet away, but showed the greatest sensitivity to dial face orientation.

Instrument E is a prototype which appears to be independent of orientation of the dial face.

These results accord with those of Nunn and Ezi-Ashi (1962).

The measurements recorded from the respirometers on the Starling pump–drum rig are shown in table III. The registered expired volume was always larger than the inspired volume and the former was always closer to the calculated volume displaced. The accuracy of the inspired volume measurement became progressively worse as the inspired volume decreased. The accuracy of the expired volume remained high even at tidal volumes as small as 100 ml.

TABLE III. *The result of connecting pairs of the four respirometers in series, one measuring inspiration and one measuring expiration, in a system consisting of a Starling pump ventilating a 5-gallon drum. The instruments were arranged so that one of them had its dial vertical and the other horizontal. Two readings were taken for each position. The tests were run for exactly 25 revolutions of the crank of the pump at a speed of* 12.5 *rev* min^{-1}. *The calculated total volume for this 2-min period is shown at the head of each set of results. The accuracy of the average of each pair of readings is expressed as a percentage of this calculated total volume*

	Inspiration		Accuracy (%)	Expiration		Accuracy (%)
300 ml at 12.5 rev min^{-1} for 2 min (total = 7.5 litre)						
B Face vertical	5.53	5.53	73.7	7.25	7.15	96.0
D Face horizontal	5.84	5.84	77.8	8.82	8.75	117.1
B Face horizontal	5.5	5.5	73.3	7.55	7.5	100.3
D Face vertical	6.6	6.6	88.0	7.46	7.45	99.4
200 ml at 12.5 rev min^{-1} for 2 min (total = 5 litre)						
B Face vertical	3.08	3.08	61.6	4.83	4.85	96.8
D Face horizontal	3.36	3.36	67.2	5.26	5.3	105.6
B Face horizontal	3.0	3.03	60.3	5.05	4.92	99.7
D Face vertical	3.25	3.25	65.0	5.08	4.92	100.0
100 ml at 12.5 rev min^{-1} for 2 min (total = 2.5 litre)						
B Face vertical	0.55*	0.59	22.8	2.35	2.35	94.0
D Face horizontal	0.6	0.56	23.2	2.5	2.5	100.0
B Face horizontal	0.4	0.4	16.0	2.45	2.35	96.0
D Face vertical	0.3	0.3	12.0	2.6	2.5	102.0
300 ml at 12.5 rev min^{-1} for 2 min (total = 7.5 litre)						
A Face vertical	5.88	5.84	78.1	7.2	7.28	96.5
C Face horizontal	5.8	5.83	77.5	7.75	7.8	103.7
A Face horizontal	5.56	5.58	74.3	7.52	7.72	101.6
C Face vertical	5.79	5.83	77.5	7.42	7.6	100.1
200 ml at 12.5 rev min^{-1} for 2 min (total = 5 litre)						
A Face vertical	3.26	3.25	65.1	4.84	4.8	96.4
C Face horizontal	3.16	3.16	63.2	5.23	5.18	104.1
A Face horizontal	3.08	3.05	61.3	5.06	5.15	102.1
C Face vertical	3.23	3.22	64.5	5.01	5.1	101.1
100 ml at 12.5 rev min^{-1} for 2 min (total = 2.5 litre)						
A Face vertical	0.77	0.72	29.8	2.5	2.52	100.4
C Face horizontal	0.55	0.5	21.0	2.65	2.67	106.4
A Face horizontal	0.74	0.71	29.0	2.58	2.58	103.2
C Face vertical	0.6	0.52	22.4	2.55	2.56	102.2

* Stalled.

Although one instrument (B) stalled during one of the smallest volume tests, the measurements from all the instruments at the smallest inspired volumes were more than four times less than they should have been, while the measured expired volumes remained close to the calculated swept volume.

Although the first test showed that the minimum flow rates from each instrument were different (table II), this difference between the instruments is not evident in table III and neither was the effect of the orientation of the instrument, except in the case of instrument B, which stalled once when the more sensitive hand had to be rotated against the effect of gravity.

These results suggest that it is not possible to rely directly on the reading from these instruments with spontaneously breathing patients with low tidal volumes, such as may occur in patients breathing high concentrations of halothane spontaneously.

The effect is less likely to occur if the lungs are ventilated artificially, particularly with the respirometer in the expiratory line as the initial flow rate from the patient will be high at the moment of opening of the expiratory valve.

CONCLUSIONS

The Wright respirometer is generally accurate when presented with flow patterns with a high initial flow rate. The accuracy deteriorates if the initial flow rate is low and accelerates only slowly. The instrument is inherently safe, however, as it will underestimate tidal volume.

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EFFETS DES DIFFERENTS MODELES DE DEBIT SUR LE RESPIROMETRE DE WRIGHT

RESUME

Les problèmes qui découlent de l'usage du respiromètre de Wright pour la mesure des petits débits associés à la précision des petits volumes ont été discutées. L'exactitude dépend beaucoup de la forme d'onde du débit qui le traverse.

DIE WIRKUNG VERSCHIEDENER STRÖMUNGSSTRUKTUREN AUF DAS WRIGHT-ATEMMESSGERÄT

ZUSAMMENFASSUNG

Probleme beim Einsatz des Wright-Atemmessgerätes fur Messungen bei den mit kleinen Volumen verbundenen geringen Durchflussmengen. Genauigkeit hangt sehr von der Wellenform des durchfliessenden Stromes ab.

EFECTO DE DISTINTOS COMPORTAMIENTOS DE FLUJO EN EL RESPIROMETRO DE WRIGHT

SUMARIO

Se hace hincapié en los problemas del uso del respirómetro de Wright para mediciones a bajos ritmos de flujo asociados con pequeños volúmenes. La exactitud depende mucho de la forma de la onda del flujo pasa a través del aparato.

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INCREASED CARBON DIOXIDE PRODUCTION IN TWO PATIENTS WITH MALIGNANT HYPERPYREXIA AND ITS CONTROL BY DANTROLENE

F. LIEBENSCHÜTZ, C. MAI AND V. W. A. PICKERODT

SUMMARY

Two patients with successfully treated malignant hyperpyrexia are reported. Carbon dioxide output, calculated from the respiratory minute volume and Pa_{CO_2}, was found to be greatly increased in both patients. In the patient who received dantrolene 7.5 mg kg^{-1} the carbon dioxide output decreased rapidly to normal values, whereas in the other patient carbon dioxide output remained increased for several hours.

Dantrolene sodium, a substance related to diphenylhydantoin, has been suggested as a specific drug for the treatment of malignant hyperpyrexia (MH) and animal experiments and *in vitro* muscle investigations indicate its usefulness in treating this condition (Ellis and Bryant, 1972; Ellis, Simpson et al., 1975; Harrison, 1975, 1977; Anderson and Jones, 1976; Gronert, Milde and Theye, 1976; Austin and Denborough, 1977; Hall, Lucke and Lister, 1977).

While Gronert and Theye (1976) showed, in porcine MH, an increase in oxygen consumption and carbon dioxide and lactate production, there are few reports on the metabolic changes in human MH.

We report two patients with MH who were treated (in addition to the Britt (1972) scheme) with dopamine and (the second patient) with dantrolene sodium.

CASE REPORTS

Case 1

An apparently healthy 29-yr-old male (body weight 61 kg) underwent surgery for acute appendicitis. His surgical history was limited to an uneventful haemorrhoidectomy performed 4 weeks earlier under general anaesthesia. The rectal temperature before operation was 38.4 °C. Premedication comprised pethidine 50 mg, promethazine 25 mg and atropine 0.5 mg i.m.

Anaesthesia was induced at 14.45 h with thiopentone 450 mg followed by suxamethonium 80 mg. Following a difficult intubation of the trachea, the pressure was 130/80 mm Hg and the heart rate 64 beat min^{-1}. Artificial ventilation was performed with halothane 2.0% and 66% nitrous oxide in oxygen in a semi-closed circuit (total fresh gas flow 6 litre min^{-1}). At 15.00 h, a supplementary dose of suxamethonium 40 mg was given and the halothane concentration was reduced to 1.5%.

Cyanosis was first detected at 15.15 h when the heart rate had increased to 100 beat min^{-1}. The fresh gas flow was increased to 8 litre min^{-1} and FI_{O_2} to 0.5. By 15.30 h heart rate had increased to 144 beat min^{-1}, and the arterial pressure had decreased to 100/80 mm Hg. MH was suspected and ventilation of the lungs with 100% oxygen was commenced. The carbon dioxide absorbers were changed and the surgeon asked to terminate the operation, which he did at 16.05 h. At this time, heart rate was 140 beat min^{-1}, arterial pressure 120/80 mm Hg and rectal temperature 43 °C.

The initial treatment comprised: surface cooling with iced water; ventilation with 100% oxygen; sodium bicarbonate 200 mmol i.v.; mannitol 50 g i.v.; frusemide 120 mg i.v.; 5% glucose 500 ml i.v. containing procaine–HCl 40 mg; Ringer solution 1000 ml i.v. and glucose 10% with soluble insulin 24 units.

Later therapy consisted of: prednisolone 1 g i.v.; dopamine 180 µg/min^{-1} i.v.; noradrenaline 5–15 µg min^{-1} i.v., and insulin i.v.

Under this treatment the patient was transferred to the intensive care unit.

At 18.00 h the rectal temperature was 39 °C, and urinary output was 700 ml. At 18.30 h the patient was comatose, but was breathing spontaneously (with

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tachypnoea) and reacting to pain. He was cyanosed and there was increased muscle tone. The rectal temperature had decreased to 33 °C, heart rate was 130 beat min^{-1} with an arrhythmia, arterial pressure was 100/60 mm Hg and the serum creatine phosphokinase concentration was 520 i.u. litre^{-1}.

The further course of events was complicated by body temperature changing between 30 and 38 °C and development of cardiac insufficiency with a decrease in systolic arterial pressure to 60 mm Hg and an increase in c.v.p. to 25 cm H_2O, which made the continuous administration of dopamine and noradrenaline necessary. A further i.v. infusion of frusemide and procaine-HCl 500 mg in 500 ml 5% glucose was given. Suspected intravascular coagulation (decrease of the platelet count and plasma fibrinogen) was treated with heparin 2000 units every 2 h. Forced diuresis with dopamine and frusemide led to an urine output of 9120 ml in 12 h and this prevented an increase in serum creatinine. The metabolic acidosis (smallest standard bicarbonate recorded was 13.1 mmol litre^{-1}) made necessary a total administration of sodium bicarbonate 700 mmol. Despite the infusion of insulin 4 u. h^{-1} hyperglycaemia with blood sugar concentrations of 87 mmol litre^{-1} occurred. The smallest serum potassium concentration was 1.7 mmol litre^{-1} and potassium chloride 370 mmol was infused.

Nine hours after the end of the operation, the patient regained consciousness and on the first day after operation the endotracheal tube was removed. For several days the patient complained of muscle pains. The abnormally increased serum enzyme activities of c.p.k. (maximal at 16 h, 4449 i.u. litre^{-1}), s.g.o.t. and s.g.p.t. decreased over the next few days. On the 6th day after operation, the patient was discharged from the intensive care unit.

Case 2

A 38-yr-old primigravida (body weight 70 kg) was anaesthetized for Caesarean section. As a child, she underwent an operation for a tumour of the right tibia, performed under uneventful hexobarbitone–ether anaesthesia. Anaesthesia was induced at 10.30 h with methohexitone 50 mg followed by suxamethonium 100 mg. Endotracheal intubation was performed with difficulty because of muscle rigidity and was accomplished only after further doses of methohexitone 110 mg and suxamethonium 100 mg. Subsequently, heart rate was 80 beat min^{-1} and systolic arterial pressure 160 mm Hg. Artificial ventilation of the lungs was with 66% nitrous oxide in oxygen at a fresh gas flow of 3 litre min^{-1} into a semi-closed circuit.

At 10.55 h a girl weighing 3350 g was delivered with an Apgar score at 1 min of 3, and at 5 min of 10. Following the delivery further muscle relaxation was achieved with alcuronium 8 mg and the inspired gas was changed to 1.0% halothane in nitrous oxide in oxygen.

At 11.15 h peripheral cyanosis was noticed and the patient developed tachycardia (160 beat min^{-1}), with a systolic arterial pressure of 120 mm Hg. Rectal temperature was 38 °C. MH was suspected; by 11.30 h the rectal temperature had increased to 39 °C and the systolic arterial pressure had decreased to 80 mm Hg with a heart rate of 150 beat min^{-1}. The lungs were hyperventilated with 100% oxygen.

The operation ended at 11.35 h, at which time the rectal temperature was 39 °C, heart rate 180 beat min^{-1} and systolic arterial pressure less than 100 mm Hg.

The patient was transferred to the intensive care unit where she was found to be comatose but reacting to pain. The pupils were moderately dilated and did not react to light. The patient was still cyanosed, with a sinus tachycardia of 185 beat min^{-1}, systolic pressure 100 mm Hg, rectal temperature 40 °C and c.p.k. value of 420 i.u. litre^{-1}. Initial treatment comprised: surface cooling with iced water; thiopentone 225 mg in five increments; ventilation with 100% oxygen at a minute volume of 21 litre min^{-1}; sodium bicarbonate 250 mmol i.v.; mannitol 50 g i.v.; dexamethasone 40 mg i.v.; 5% glucose 500 ml i.v. with lignocaine 1 g; heparin 1000 units i.v. every 2 h; dopamine 180 μg min^{-1}; continuous infusion of fentanyl and droperidol; infusion of soluble insulin 4–12 unit h^{-1}; frusemide 100 mg i.v.; infusion of dantrolene solution 1050 ml, equivalent to 525 mg or 7.5 mg kg^{-1} of dantrolene. The dantrolene solution was made up as described by Gronert, Mansfield and Theye (1978).

At 13.10 h the patient regained consciousness. The pupils reacted to light and there was no cyanosis. The rectal temperature was 37.5 °C, the heart rate 130 beat min^{-1} and the systolic arterial pressure 110 mm Hg, with no signs of cardiac insufficiency. With further doses of frusemide, urinary output was 5500 ml/12 h. Artificial ventilation for the subsequent period was performed with $F_{I_{O_2}}$ 0.6 adjusted according to the arterial blood-gas analyses, and a respiratory minute volume of approx. 8 litre min^{-1}. Serum potassium concentrations fluctuated between 2.5 and 5.4 mmol litre^{-1} and over the first 12 h potassium chloride

280 mmol was infused. The smallest standard bicarbonate concentration recorded was 15.2 mmol litre^{-1} and a total of sodium bicarbonate 875 mmol was infused to correct metabolic acidosis. The greatest blood glucose concentration recorded was 31 mmol litre^{-1}.

Because of intra-abdominal bleeding the patient underwent two further operations on the following day. General anaesthesia with fentanyl and nitrous oxide in oxygen without muscle relaxation was uneventful. As the patient developed respiratory insufficiency and an increased body temperature, artificial ventilation was required for 9 days, and after removal of the tracheal tube she was transferred on the 12th day to a gynaecological ward, where she complained of headache for another few days. Subsequently mother and child progressed well.

DISCUSSION

Both patients exhibited the typical features of MH after anaesthesia with halothane and suxamethonium, with the characteristic signs of high temperature, muscular rigidity, tachycardia, hyperventilation and cyanosis. Both had increased serum c.p.k. values (max. 4000–5000 i.u. litre^{-1}). Some of the relatives of the second patient had increased c.p.k. values, but serum c.p.k. concentrations in the investigated relatives of the first patient were normal. However, the value of c.p.k. as a screening test for susceptibility to MH has been questioned by Ellis, Clark and others (1975).

Important in the prognosis of this condition is not only the maximum body temperature or duration of exposure to halothane, as suggested by Britt and Kalow (1970), but also the ability to monitor vital functions and to provide continuous intensive care. Typical hyperkalaemia was observed at the beginning in both patients (5.5 and 6.8 mmol litre^{-1}); even more important, however, was the subsequent hypokalaemia (2.5 and 1.7 mmol litre^{-1}) which was difficult to correct despite frequent monitoring and continuous infusions of K^+ 370 and 280 mmol/12 h respectively. Although metabolic studies are possible in experimental animals (Gronert and Theye, 1976; Gronert et al., 1978), it is not possible to obtain precise measurements in MH occurring clinically. However, it remains uncertain if animal models closely represent human MH.

To obtain an index for the increase of aerobic metabolism, we calculated the product of respiratory minute volume and arterial $P\text{CO}_2$ as follows: Assuming a dry barometric pressure of 95 kPa and that arterial $P\text{CO}_2$ equals alveolar $P\text{CO}_2$:

$$\text{CO}_2\ \text{output (ml min}^{-1}) = \text{alveolar ventilation (ml min}^{-1}) \times \frac{Pa_{\text{CO}_2}}{95}$$

Measurement of alveolar ventilation and functional deadspace is difficult clinically in a patient with MH. Functional deadspace is influenced by age, size of the patient, position, duration of inspiration, underlying lung disease, anaesthesia and apparatus deadspace. To allow for all factors we have assumed V_D/V_T approximately 40%. In the second patient the highest index (minute volume × Pa_{CO_2}) was 160 (fig. 1), thus we can estimate the carbon dioxide output to be of the order of 1000 ml min^{-1}. The normal carbon dioxide

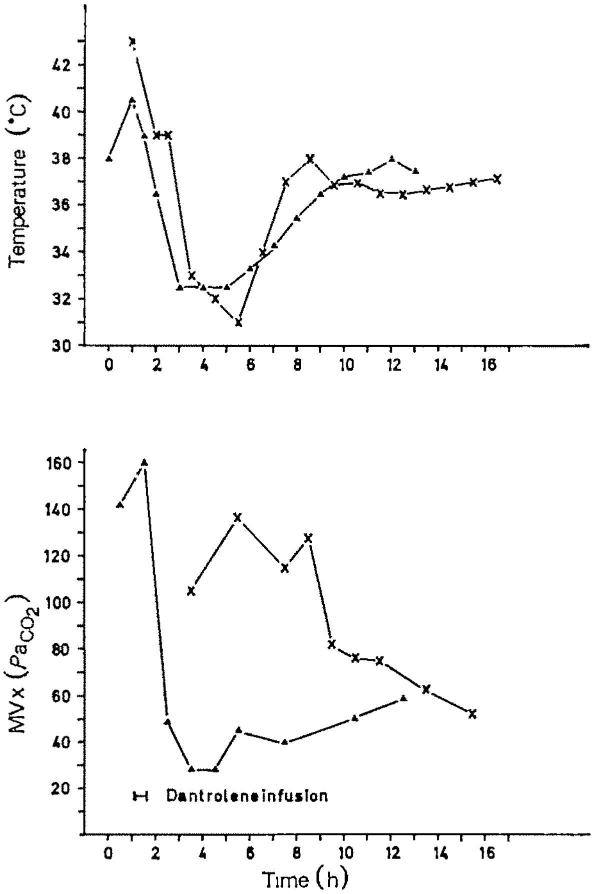

FIG. 1. Rectal temperature of two patients with malignant hyperpyrexia (upper part) and index of carbon dioxide output (minute volume × Pa_{CO_2}) (lower part). × = first patient; ▲ = second patient, who received dantrolene 7.5 mg kg^{-1}.

output for a patient of her age and weight would be about 150 ml min^{-1} (Nunn, 1977).

However, this estimate does not take into account the following: At the time of measuring the index of 160, the patient had received 8.4% sodium bicarbonate 500 ml, which corresponds to a carbon dioxide output from the lungs of about 11 000 ml. The body temperature of the patient at that time was about 4 °C above normal, which would result in an increased carbon dioxide output of about 40%. The different solubility for carbon dioxide in plasma at different body temperatures has not been allowed for. Under non-steady-state conditions carbon dioxide production is not in equilibrium with carbon dioxide output.

However, as may be seen from figure 1, the first patient showed a greatly increased carbon dioxide output even though his body temperature was between 31 and 32 °C. This output must be related to increased oxygen consumption.

We cannot assess the extent of anaerobic metabolism, as we did not measure plasma lactate concentrations, but it seems likely that the low standard bicarbonate values of our patients resulted from lactic acidosis. However, on the basis of their animal experiments Gronert and Theye (1976) discussed an increase of lactate that could be non-hypoxic in origin and occurred before changes in oxygen consumption, temperature and $P\text{CO}_2$.

The data on our two patients suggest that it is necessary to treat MH in the acute phase by controlled ventilation with 100% oxygen, insertion of an arterial cannula for arterial pressure measurement and serial blood-gas analyses and by continuous measurement of end-tidal carbon dioxide concentration to adjust the respiratory minute volume to the changing demand of the patient.

Dantrolene sodium increases the armamentarium of the anaesthetist in treating patients with MH. Its site of action is in the muscle cell, where it inhibits the liberation of calcium ions from the sarcoplasmic reticulum (Ellis and Carpenter, 1974). The efficiency of the drug has been shown in numerous experiments *in vivo* and *in vitro* (Ellis and Bryant, 1972; Ellis, Simpson et al., 1975; Harrison, 1975, 1977; Gronert, Milde and Theye, 1976; Austin and Denborough, 1977; Hall, Lucke and Lister, 1977). These encouraged us to use the drug for our second patient. The dose used corresponded to that of Gronert, Milde and Theye (1976) and Hall, Lucke and Lister (1977). There was no significant difference in the course of the temperature changes in both patients (fig. 1). By massive surface cooling, body temperature was decreased to hypothermic values in both patients fairly quickly. However, there was a marked difference in the curve of the index for carbon dioxide output, which was almost within normal limits shortly after the administration of dantrolene to the second patient, whereas it remained increased for several hours in the first patient, who did not receive dantrolene. This confirms the experimental findings in MHS pigs of Gronert, Milde and Theye (1976).

Marked differences also existed between both patients with regard to the degree of cardiac insufficiency. This was so severe for the first patient as to require the infusion of noradrenaline. This may be related to the recent finding of Gronert and others (1978), who found increased myocardial oxygen consumption in MHS pigs.

Although it is difficult to relate any differences between the two patients to the administration of dantrolene, our data support the experimental evidence that the drug is specific for the treatment of malignant hyperpyrexia and justify its use in humans.

ACKNOWLEDGEMENTS

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AUGMENTATION DE LA PRODUCTION DE GAZ CARBONIQUE CHEZ DEUX MALADES SOUFFRANT D'HYPERPYREXIE MALIGNE ET SA REDUCTION PAR LE DANTROLENE

RESUME

On signale dans cet article le cas de deux malades atteints d'hyperpyrexie maligne qui ont été traités d'une manière satisfaisante. La production de gaz carbonique, calculée à partir du débit cardiaque et la Pa_{CO_2}, ont été trouvées trop importantes chez ces deux malades. Dans le cas du malade qui a reçu du dantrolène à raison de 7,5 mg kg^{-1}, la production de gaz carbonique a décru rapidement pour retourner à des valeurs normales, alors que dans le cas de l'autre malade, la production de gaz carbonique est restée très élevée pendant plusieurs heures.

ERHÖHTE KOHLENDIOXYDPRODUKTION IN ZWEI PATIENTEN MIT BÖSARTIGER HYPERPYREXIE UND IHRE EINSCHRÄNKUNG DURCH DANTROLEN

ZUSAMMENFASSUNG

Es wird über zwei Patienten mit erfolgreich behandelter bösartiger Hyperpyrexie berichtet. Es wurde festgestellt, dass die aus dem respiratorischen Herzminutenvolum und Pa_{CO_2} errechnete Kohlendioxydproduktion in beiden Patienten beträchtlich erhöht war. In dem Patienten, der 7,5 mg/kg Dantrolen erhielt, sank die Kohlendioxydproduktion schnell auf normale Werte ab, während in dem anderen Patienten die Kohlendioxydproduktion mehrere Stunden lang auf dem erhöhten Niveau verblieb.

AUMENTO DE LA PRODUCCION DE DIOXIDO DE CARBONO EN DOS PACIENTES CON HIPERPIREXIA MALIGNA Y SU CONTROL POR DANTROLENO

SUMARIO

Se informó de dos pacientes con hiperpirexia maligna cuyo tratamiento tuvo éxito. Se comprobó que la producción de dióxido de carbono, calculada a partir del volumen respiratorio por minuto y del Pa_{CO_2}, había aumentado substancialmente en ambos pacientes. En el paciente que recibió 7,5 mg kg^{-1} de dantroleno, la producción de dióxido de carbono bajó rápidamente hacia valores normales, mientras que, en el otro, la producción de dióxido de carbono se mantuvo en aumento durante varias horas.

Br. J. Anaesth. (1979), **51**, 905

AN ENDOBRONCHIAL CUFF INDICATOR FOR USE IN THORACIC SURGERY

A. V. JENKINS

SUMMARY

A simple apparatus and a method are described by which an exact end-point can be attained in inflating the bronchial cuff of a double-lumen tube, and accidental collapse of the cuff detected.

Accurate inflation of the bronchial cuff of an endobronchial tube is important. Jenkins and Clarke (1958) advocated double-lumen endobronchial tubes during thoracic surgery. They used the catheter designed by Carlens (1949). Robertshaw (1962) introduced a low-resistance tube in right- and left-handed forms and this has been popular. Further support for the routine use of such tubes was provided by Edwards and Hatch (1965), Zeitlin, Short and Ryder (1965) and Thompson and Campbell (1973). Double-lumen tubes are now used routinely in most thoracic surgical centres in the U.K., and are of great value during thoracotomy, especially if lung conservation is being practised, for example by sleeve resection. One of the complications that may develop during the use of a double-lumen tube is that the endobronchial cuff may rupture. This may go unnoticed, with serious consequences. The problem is particularly likely with right-sided tubes, if a too small tube is chosen, and if the cuff is over-inflated. Even with a tube of optimal size, over-inflation is likely unless care is taken (Ryder, Short and Zeitlin, 1965). A visual indication of adequate and continuing cuff inflation, whereby a definite end-point is seen, is therefore a useful device.

When using a double-lumen tube the tracheal cuff is inflated in the usual way, so that there is no reflux of gas around the tube when positive pressure is applied to the airway. Inflation of the bronchial cuff of, for example, a right-sided endobronchial tube is best performed whilst the left side remains open to air, and whilst ventilating down the right side only. Reflux of gas then passes around the endobronchial cuff, back to the carina and thence out of the "tracheal" portion of the tube (out of the left side in the case of a right-sided tube). This reflux can be clearly heard and felt at the open end of the left side. The endobronchial cuff can then be inflated until reflux just fails to develop at the chosen inflation pressure, for example 30 cm H_2O. During surgery, it is often difficult to gain access for assessment of endobronchial cuff tension in the manner described above.

Figure 1 shows our apparatus for a visual and audible indication of a precise end-point for cuff inflation and a continuing indication of cuff integrity. A standard corrugated rubber catheter mount is attached to a right-angled International connection (BOC–Medishield). The other end of the catheter mount is

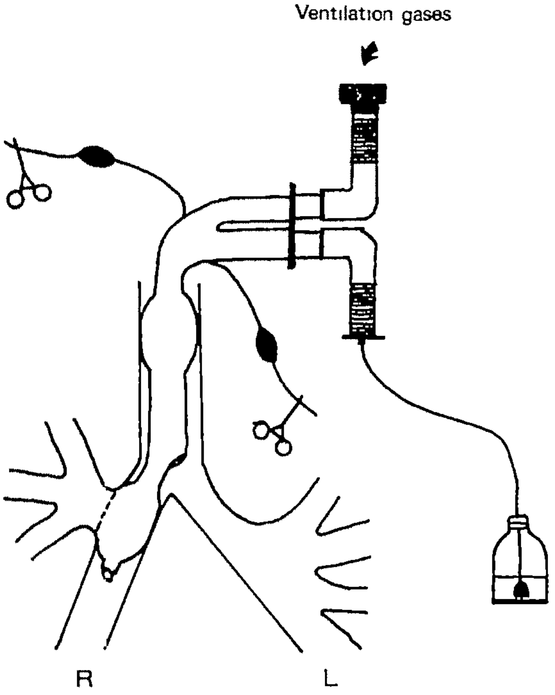

FIG. 1. Robertshaw right-sided tube with cuff indicator attached.

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attached to a 3-mm International series endotracheal tube connector. This in turn feeds into a piece of standard narrow-bore oxygen delivery tubing cut to a suitable length. The distal end of the oxygen tube is attached to a suitable "sinker" (a spare Nosworthy endotracheal tube connector of small size). The sinker is immersed below the surface in a 100-ml glass bottle containing about 30 ml of coloured water.

Using a right-sided double-lumen tube, the apparatus is put into use when the left lung is excluded from the circuit by the usual clamping of the left side of the double catheter mount. At this time, during the inflation phase, gases pass back around the endobronchial cuff to the carina, and thence to the open end of the left endobronchial tube where they escape through the apparatus and cause bubbling in the indicator bottle. The endobronchial cuff is inflated until the bubbling during inflation just ceases. Residual gases trapped within the *left* lung may still cause bubbling for a while, but this is not readily mistaken for inadequate cuff inflation because the residual air escapes during both the inspiratory and expiratory phases of ventilation. Also, this escape of trapped gases ceases after a short time.

It is important that the indicator bottle should be positioned well below the level of the patient's carina, in order to prevent siphoning of the indicator fluid from the bottle into the patient's chest.

Following satisfactory inflation of the bronchial cuff the apparatus may be detached, so that suction can be applied down the open end of the tube in the usual way. During prolonged one-lung procedures such as transthoracic oesophagectomy with colon graft, it has been found advantageous to leave the indicator connected. Should a leak develop in the bronchial seal, the appearance and sound of bubbling in the indicator bottle will alert the anaesthetist. In this way the apparatus serves as an additional safety factor.

The device has been in use for many months in the Regional Thoracic Surgical Unit at the East Birmingham Hospital and has been widely accepted by consultant and trainee staff. Some form of label may be usefully attached to the apparatus in order to avoid dismantling and loss of the assembled equipment.

ACKNOWLEDGEMENTS

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MANCHON ENDOBRONCHIQUE SERVANT D'INDICATEUR A UTILISER POUR LA CHIRURGIE THORACIQUE

RESUME

On décrit dans cet article un appareil et une méthode simples grâce auxquels on peut atteindre un point terminal précis lors de l'inflation du manchon bronchique d'un tube à double passage et détecter ainsi tout affaissement accidentel du manchon.

EINE ENDOBRONCHIALMANSCHETTE ALS INDIKATOR BEI THORAXCHIRURGIE

ZUSAMMENFASSUNG

Es wird ein einfaches Gerat und ein Verfahren beschrieben, mittels deren beim Aufpumpen der Bronchialmanschette einer Doppellumenröhre ein genauer Endpunkt erreicht und ein akzidenteller Manschettenkollaps entdeckt werden kann.

UN INDICADOR PARA BRAZIL NEUMATICO ENDOBRANQUIAL PARA USO EN CIRUGIA TORACICA

SUMARIO

Se describe un aparato sencillo y un método mediante los cuales podrá obtenerse un punto final exacto en la inflación del brazal neumático de un tubo de doble abertura, así como la detección del colapso del brazal.

Br. J. Anaesth. (1979), **51**, 907

CORRESPONDENCE

ACCURACY OF ANAESTHETIC GAS FLOWMETERS

Sir,—I would like to comment on some of the observations and correct certain statements in the recent article by Drs Waaben, Stokke and Brinkløv (1978).

On the subject of accuracy, it is interesting to note that, without definition, the writers invariably quote errors as percent of measured value. This is justifiably the user point of view. However, if a scale is nearly linear, the discrimination at the lowest readings makes such values questionable. Manufacturers, for their part, want to present their products in the most favourable but honest manner. Thus the accuracy quoted is likely to be as good as can be achieved by the manufacturing methods practised. Ideally the "confidence" in the accuracy should be the same at all readings. ("Confidence" is the degree of certainty that the reading is accurate within the stated tolerance.)

The simple statements of accuracy, "percent of indicated value" and "percent of full scale reading", both lead to low confidence at each end of the range of scaled values. A better solution is to express the accuracy as a combination of two or more tolerances. Thus one may express it as "$x\%$ of indicated value $+y\%$ of full scale reading" or "$x\%$ of indicated value, *or* y mm positional error, whichever is the greater". There are many other combinations.

The statement about the accuracy of flowmeters being ±2% (of indicated value) even when new, does not stand up to close scrutiny at low flows because of discrimination.

It may be presumption, but figure 1 showed flowmeters made by the former Rotameter Manufacturing Co. Ltd (England), with which I have been connected. This company is now owned by Fisher Controls Limited and continues to make anaesthetic flowmeters. However, at no time have we declared the calibration to be at 22 °C. It has until now been at 15 °C.

Extensive work into the characteristics of the Variable Area devices has shown that the formula correcting for change of conditions is not expressed adequately by the density (turbulent flow) formula at these rates of flow.

The method of testing the flow rates with the Soap Film Burette is good when its features are recognized. For instance, if dry gas enters the burette, water is evaporated from the walls of the cylinder and the gas leaves it humidified to an uncertain extent, possibly of greater volume and at lower temperature. These uncertainties should be corrected.

In the discussion, the difficulties of obtaining a steady reading were mentioned. If the float misbehaves its mean position does not indicate the mean rate of flow. Misbehaviour can occur from the following: (i) float damage: wear, distortion; (ii) tube not vertical; (iii) dirt: on float, on tube bore; (iv) flow deviations: erratic or pulsating, asymmetry; (v) mechanical vibration; (vi) static charges.

Any float misbehaviour will aggravate (vi) by frictional charging when the float rubs against the tube. Commonly, the static just causes the float to continue fluttering even if the original fault is corrected. Modern treatment of the glass now eliminates the static nuisance.

From my own experience I would suggest that the spread of results arises from two main factors: float behaviour and inaccurate correction for temperature and pressure. Both faults would show mostly at the lower flows and the most likely cause of float misbehaviour would be vertical setting.

In the design of these flowmeters a number of conflicting interests had to be satisfied. For instance, a high ratio of maximum to minimum flow gives rise to a very low tube to float clearance at minimum. This demands very precise vertical setting. Again a demand for the float to be "visible", that is large, means that the annulus is small, again requiring precise vertical setting.

I have encountered all the faults mentioned in the last paragraph of the article, but I suspect that thoughtless cleaning may be prevalent. Floats can be distorted in handling. Removing dirt can also mean modification of the critical head edges which changes the calibration, and replacing floats in the wrong tubes can occur.

E. A. Hodge
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REFERENCE

Waaben, J., Stokke, D. B., and Brinkløv, M. M. (1978). Accuracy of gas flowmeters determined by the bubble meter method. *Br. J. Anaesth.*, **50**, 1251.

Sir,—We were interested to read the comments by Mr Hodge on our article (Waaben, Stokke and Brinkløv, 1978) and are pleased to have the opportunity of replying.

First, we have been misinterpreted as expressing errors in percent of measured value. Instead, the designation "percentage deviation from preset flow rate" has been used throughout the paper, a term for which no further definition seems necessary. However, no matter how flowmeter accuracy is expressed, it is important for the anaesthetist to know how his flowmeters are functioning in daily clinical practice. Our investigation was designed to study this aspect.

The manufacturer has told us (GEC–Marconi Process Control Ltd, 1978, personal communication) that, in practice, all anaesthetic tubes are inspected with the aid of Master flowmeters using series calibration, the inspection tolerances applied being $\pm 0.5\% \times (5\%$ of indicated flow $+ 0.5\%$ of full scale reading). Expressing the accuracy in this way, we found that 71.1% of the measurements exceeded the limits at oxygen presettings of less than 1 litre min^{-1}, but above 1 litre min^{-1} 37.8% were still outside the limits. The corresponding figures for flows of nitrous oxide alone and in combination with oxygen were 21.3% and 21.7% respectively. It would be interesting to know how the Master tubes are calibrated.

We can only agree that a flowmeter accuracy of ±2% does not stand up to close scrutiny at any flow rates, especially not at low flows. This tolerance, however, is quoted from a well-known textbook (Macintosh, Mushin and Epstein, 1958).

The flowmeters investigated were made by the Rotameter Manufacturing Co. Ltd. As stated in the article, flows were corrected to 22 °C in accordance with the information given by our local supplier. The correction factor from 22 °C to

15 °C is approximately 2%, which is not of any clinical significance.

We are fully aware that the formula for turbulent flow does not completely correct for the change of conditions in the tube concerning the various flow rates. However, we regarded it as the most applicable and adequate formula in practice and sufficiently satisfactory from a scientific point of view.

The gas entering the burette was fully saturated with water vapour. The temperature was measured at the outlet of the burette and the barometric pressure recorded continuously during measurements. As stated in our paper, complete correction was made for the vapour pressure of water, and the calculated flows were corrected to the calibration standard reported by the supplier (22 °C; 101 kPa).

Performing measurements with the flowmeters in a vertical setting is obviously fundamental; all measurements were made on a plane, and a truly vertical setting was controlled by means of a spirit level.

Thus, we are still of the opinion that our observations are valid.

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D. B. Stokke
M. M. Brinkløv
Odense, Denmark

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FIRE AND EXPLOSION HAZARDS IN OPERATING THEATRES: A REPLY AND NEW EVIDENCE

Sir,—Vickers (1978) reviewed the theoretical explosion risk from the use of nitrous oxide for laparoscopy (Robinson, Thompson and Wood, 1975), with the aid of calculations made by Mapleson. He concluded that the risk was not a credible one.

Our attention has been drawn to the occurrence of such an explosion which resulted in the death of the patient. The patient was a 25-yr-old mother of two children admitted to hospital for laparoscopic sterilization. The peritoneal cavity was inflated with 4–5 litre of nitrous oxide. The surgeon passed the single-puncture operating laparoscope and visualized the pelvic viscera. The coagulating forceps was introduced through the laparoscope and the Fallopian tube was grasped; the diathermy foot switch was then pressed by the assistant. The surgeon, noticing that no coagulation was occurring, checked the leads and repeated the procedure. The diathermy voltage was increased. As no coagulation of the tubes was taking place, the surgeon decided to abandon the procedure and he asked his assistant to take his foot off the foot switch. As he was withdrawing the coagulating forceps through the laparoscope, he heard a bang like a balloon bursting.

The patient suffered an immediate cardiac arrest from which she could not be revived. The assistant was at the vaginal end and was thrown back by the blast. No flammable agent had been used for cleaning or sterilizing the laparoscope.

At postmortem, the diaphragm was found to have two large holes on both sides involving the muscular portion; the muscles were torn and contracted. There was about 500 ml of blood in the abdominal cavity. The stomach was normal and there were no perforations of the small and large intestines. The mesentery was normal and the liver and spleen were undamaged. The anterior abdominal wall and the recti muscles were completely torn from the inner surface and there was a black discolouration noted in the muscle tissue around the umbilicus. Histological examination of this tissue showed no evidence of an electrical burn. The laparoscope was bent, the Verres needle was broken in two and the intra-uterine cannula was bent.

We have had our attention drawn to another explosion occurring when using nitrous oxide to inflate the peritoneum during laparoscopic diathermy, but we have been unable to obtain any clinical details. [*Note added in proof.* The report of this case has been published: El-Kady, A. A., and Abd-el-Razek, M. (1976). Intraperitoneal explosion during female sterilization by laparoscopic electrocoagulation. A case report. *Int. J. Gynecol. Obstet.*, **14**, 487.]

Mapleson's calculations in the appendix to Vicker's review (1978) assume that hydrogen and methane only diffuse after production of the pneumoperineum, but, in fact, the production of these gases will be near to a steady-state. They will be diffusing all day and every day. The adipose tissue in the peritoneal cavity will act as a reservoir which can "outgas" on introduction of nitrous oxide into the cavity. All this, however, is mere speculation.

We drew attention to a potential hazard (Robinson, Thompson and Wood, 1975) and are now aware of an actual hazard.

J. S. Robinson
John M. Thompson
A. W. Wood
Birmingham

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Robinson, J. S., Thompson, S. J. M., and Wood, A. W. (1975). Laparoscopy explosion hazards with nitrous oxide. *Br. Med. J.*, **3**, 764.

Vickers, M. D. (1978). Fire and explosion hazards in operating theatres. *Br. J. Anaesth.*, **50**, 659.

CEREBRAL BLOOD FLOW AND ETOMIDATE

Sir,—We read with interest the paper by Renou and colleagues (1978) and would like to make the following comments.

When the author says that, to her knowledge, there have been no reports on the effects of etomidate on cerebral blood flow, we can inform you that we published a paper showing that after etomidate 0.3 mg/kg body weight c.b.f. decreased significantly, except in the fronto–orbital region.

Although we measured the oxygen content of cerebral venous blood sampled at the internal jugular bulb (van Aken and Rolly, 1976), we think it is incorrect to calculate CMRo$_2$ by multiplying the data for *regional* flow and arterio–venous oxygen content difference of blood which is assumed to be representative of the whole brain.

J. van Aken
G. Rolly
Ghent, Belgium

REFERENCES

van Aken, J., and Rolly, G. (1976): Influence of etomidate, a new short-acting anaesthetic agent, on cerebral blood flow in man. *Acta Anaesthesiol. Belg.*, **27** (Suppl.), 175.

Renou, A. M., Vernheit, J., Macrez, P., Constant, P., Billerey, J., Khadaroo, M. Y., and Caillé, J. M. (1978). Cerebral blood flow and metabolism during etomidate anaesthesia in man. *Br. J. Anaesth.*, **50**, 1047.

TREATMENT OF SNAKE BITE

Sir,—With regard to the recent letter by Dr Sutherland and myself (Brophy and Sutherland, 1979), recent research conducted at the Commonwealth Serum Laboratories (C.S.L.), Melbourne, has shown that firm pressure applied over the bitten area significantly delays the movement of venom. When pressure is combined with immobilization of the limb, very little venom reaches the blood stream. Based on this work, the rational first aid management of snake bite becomes:

(1) Immediately apply a firm broad bandage around the limb to cover the bitten area. This should be as tightly applied as for the binding of a sprained ankle. As much of the limb as possible should be included in the bandage. Crepe bandages are ideal but any flexible material may be used in an emergency.

(2) Immobilize the limb with a splint—a piece of wood or any rigid object.

(3) Bring transport to the victim where possible.

(4) Leave the bandages and splint on until medical care is reached.

Do not cut or excise the bitten area.

Do not wash the bitten area—the snake may be identified by the venom on the skin.

If the snake can be killed safely, it should be brought to hospital with the victim.

The research at C.S.L. has shown that this simple first aid treatment is as effective as an arterial tourniquet, but is more practical because it is painless, there is no risk of ischaemia and the bandage may be left in place until medical help is reached.

It is also stressed that delayed application retards movement of remaining venom—and that the bandage should be reapplied if the victim becomes ill after initial removal.

T. Brophy
Australian Resuscitation Council
Brisbane

REFERENCES

Brophy, T., and Sutherland, S. K. (1979). Use of neostigmine after snake bite. *Br. J. Anaesth.*, **51**, 264.

ACCURACY IN MORPHINE ADMINISTRATION

Sir,—Dr Rigg and his colleagues (1978) report a large variation in blood morphine concentrations after i.m. injection. They attributed this to variation in blood flow and perhaps inadvertent injection into fat rather than muscle. I believe that they have overlooked an even greater source of error, namely inaccurate dosage.

They stated that each patient received morphine 0.15 mg kg^{-1} in the upper lateral aspect of the right gluteal region. I am sure that the injection was in the prescribed place, but was the correct amount given? Simple arithmetic shows that some of the quantities had to be measured to 0.01 of a milligram. Patient 1 should have received morphine 14.25 mg, patient 6, 13.05 mg, patient 11, 7.95 mg and patient 25, 11.55 mg.

If the prescription was 0.15 mg kg^{-1} on the drug sheet, my experience in Australia and England suggests that about half the calculations will be incorrect and the wrong dose given. Proof that the correct amount was administered requires detailed description of the dispensing procedure. In Australia morphine is commonly dispensed as 10 mg ml^{-1}. Thus the 100th graduations in a tuberculin syringe are measuring 0.1 mg of morphine. If 2-ml syringes were used the nearest accurate measurement, to a marked line, is 1 mg.

Greater accuracy may be achieved by the dilution of the solution, but the greater volume of injection would cause discomfort and pain to the patient.

John Knight
Melbourne, Australia

REFERENCE

Rigg, J. R. A., Browne, R. A. Davis, C., Khandelwal, J. K., and Goldsmith, C. H. (1978). Variation in the disposition of morphine after i.m. administration in surgical patients. *Br. J. Anaesth.*, **50**, 1125.

Sir,—Dr Knight is correct in pointing out that a possible source of error in our studies was inaccuracy in calculating the dose of morphine. We recognized this at the time of the study, but did not feel that it was worthy of discussion in the paper, since our simple arithmetic did not convince us that it was an important error.

As our paper indicated, no special procedures were used to ensure greater accuracy of injection volume than might be expected if the injection was given by a properly instructed nurse. Since we were fully cognizant of this potential source of error, all patients were weighed on a scale of known precision on the day before surgery and all doses were calculated (mg and ml—morphine solution 10 mg ml^{-1}) by one of the principal investigators (J. R. A. R. or R. A. B.).

Both 3.0-ml syringes and 1.0-ml tuberculin syringes were used to measure the precise volume to the best estimate by eye, and calculated volumes were drawn up and injected by one of the investigators or a nurse instructed in the procedure by one of us. We are confident that the range of error in the estimation of the correct volume of morphine solution for injection, would be not greater than $\frac{1}{4}$–$\frac{1}{2}$ of the smallest graduation on the 3-ml syringe (a maximum probable error of 0.05 mg). The mean dose given was almost 10.5 mg. Thus, we estimate the error from this source to be about 2–5%. However, even if we assumed that the error was 10%, this could not possibly account for more than a small part of the variation of Cp_{max} and t_{max} reported. We would emphasize again the similarity of variation we observed in plasma morphine concentration to the variation of regional blood flow reported by Evans and others (1975) and suggest that the mechanisms described by us are the most likely explanation of our findings.

John R. A. Rigg
Hamilton, Ontario, Canada

REFERENCE

Evans, E. F., Proctor, J. D., Fratkin, M. J., Velandia, J., and Wasserman, A. J. (1975). Blood flow in muscle groups and drug absorption. *Clin. Pharmacol. Ther.*, **17**, 44.

TEST DOSES IN EXTRADURAL ANALGESIA

Sir,—I am sorry that Dr Stirt (Stirt, 1979) should assume that I believed glucose and lignocaine had similar molecular structures. However, both compounds cross capillary walls easily and rapidly and therefore both will move in the direction of their concentration gradients—glucose into the extradural space and lignocaine out of it. At the time of writing my previous letter (Scott, 1979), I only had the evidence of the lignocaine concentrations to make my case. However, since the publication of Dr Stirt's letter (1978), I have obtained fluid from the extradural space of four patients. It may be relevant that all were surgical patients who had received 20 ml of local anaesthetic solution—about twice the dose used in relieving labour pain. In three, the fluid was seen dripping slowly from the Milipore filter attached to the catheter end, and with gentle aspiration 0.2 ml, 0.5 ml and 1.5 ml respectively were obtained 10–15 min after injection. Although not all the fluid would have been in the extradural space, especially in the case of the two smaller volume samples, the glucose content was 0.05 mmol litre^{-1}, 1.1 mmol litre^{-1} and 4.4 mmol litre^{-1}. In the fourth patient 2 ml was obtained by spontaneous refilling of the 20-ml glass syringe attached to the Milipore filter. In this case the glucose content was 1.7 mmol litre^{-1}.

All four catheters were subsequently used for introducing extradural local anaesthetic in the period after operation and no problems of high blockade were met. Although the glucose concentrations are less than that found in Dr Stirt's case (4.94 mmol litre^{-1}) his patient had an abnormally increased blood glucose, 8.44 mmol litre^{-1} compared with the normal range of 3.6–5.8 mmol litre^{-1}.

If Dr Stirt's catheter had entered the subarachnoid space, why wasn't the glucose concentration much closer to that of the blood, because c.s.f. concentrations follow closely those of blood? How did the fluid manage to drip back when the end of the catheter was occluded? His case remains unconvincing and cannot be taken as evidence of transdural migration of the catheter.

D. B. Scott
Edinburgh

REFERENCES

Scott, D. B. (1979). Test doses in extradural analgesia. *Br. J. Anaesth.*, **51**, 808.

Stirt, J. A. (1978). Test doses in extradural analgesia. *Br. J. Anaesth.*, **50**, 1267.

—— (1979). Test doses in extradural analgesia. *Br. J. Anaesth.*, **51**, 808.

Sir,—Dr Scott does not yet seem persuaded that the case I reported (Stirt, 1978) involved transdural migration of an extradural catheter.

I found Dr Scott's study of extradural fluid glucose concentrations of some interest, as much for the questions it raises as those it answers. I must congratulate him for succeeding where I failed in obtaining what appear to be the first measurements of extradural space glucose concentrations to be reported. Yet one question remains in my mind when I look at his values. What contribution was made by local anaesthetic glucose concentration? As I noted earlier, 3% chloroprocaine contains a small but significant amount of glucose (0.39 mmol litre^{-1}). Did the local anaesthetic solution used by Dr Scott perhaps have a similar, or even greater, glucose content? This makes me suspicious of the smallest value he reports, and perhaps the others as well. Let us assume for the moment that there is indeed an appreciable movement of glucose into whatever fluid occupies the extradural space.

Dr Scott points out, correctly, that the blood glucose concentration in the case I reported was "abnormally high" (8.44 mmol litre^{-1}). This was undoubtedly a result of a continuous i.v. infusion of 5% dextrose in water which had been running for about 5 h before the administration of anaesthesia. In any case, one would expect the c.s.f. glucose not to "follow closely" but rather to be approximately 60–70% of that in blood (Tietz, 1976). Indeed, as I reported earlier, catheter fluid glucose was 4.94 mmol litre^{-1} with a simultaneous blood glucose concentration of 8.44 mmol litre^{-1}.

I attribute the fluid return past the occluded end of the catheter to the relatively high pressure in the subarachnoid space, where I believe the end of the catheter resided.

"Like ourselves . . . they see only their own shadows, or the shadows of one another, which the fire throws on the opposite wall of the cave" (Plato, 366 B.C.). I suggest that the side of the dura upon which one believes the shadow of the extradural catheter in question fell is, in the end, a matter of how one chooses to interpret the shadows of data and doubt cast by Dr Scott and myself.

J. A. Stirt
Los Angeles

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Plato (366 B.C.). *The Republic*, Book VII: 515-B. (Ed. J. D. Kaplan). New York City: Pocket Books, 1976.

Stirt, J. A. (1978). Test doses in extradural analgesia. *Br. J. Anaesth.*, **50**, 1267.

Tietz, N. W. (1976). *Fundamentals of Clinical Chemistry*, p. 242. Philadelphia: W. B. Saunders Co.

ANTICHOLINERGIC PREMEDICATION

Sir,—I am writing about the methods of the study by Mirakhur, Dundee and Connolly (1979). The statistical analysis of the data was very extensive and carefully done. They have gone to great length to show statistical significance of heart rate changes of 3 and 4 beat min^{-1}. Yet, although data are given regarding the weight of the patients involved, no attempt is made to correlate this information with changes in heart rate. Table I, for example, indicates that the difference in weight between the patients given hyoscine 1 mg orally and hyoscine 0.25 mg i.m. was 4 kg. A weight difference of greater than 10% as in this case, would almost certainly affect the clinical measurements that were made so carefully. Because the authors obviously have the data it would seem reasonable that their results be reworked on a dose/unit weight basis, as was done for the administration of the induction agent.

As an aside, it is interesting to note an initial slight decrease in heart rate at the lower dose ranges, although this is statistically insignificant.

I. J. Gilmour
Minneapolis, U.S.A.

REFERENCE

Mirakhur, R. K., Dundee, J. W., and Connolly, S. D. R. (1979). Studies of drugs given before anaesthesia. XVII: Anticholinergic premedication. *Br. J. Anaesth.*, **51**, 339.

Sir,—Even though some small changes in heart rate were shown to be statistically significant, no clinical significance was attached to such changes. The study was primarily done to assess the overall need of anticholinergic premedication in patients undergoing minor surgery and as such drugs were not administered on a weight basis.

However, Dr Gilmour's comment has aroused our interest in this subject and we plan to present the results in a separate communication.

R. K. Mirakhur
J. W. Dundee
Belfast

ADVERSE REACTIONS TO ANAESTHETIC AGENTS

Sir,—There has been much recent interest in the mechanisms which underlie adverse reactions to i.v. anaesthetic drugs. Watkins and colleagues (1976) have shown convincingly that complement activation via the alternate pathway is a frequent mechanism underlying the adverse reaction to Althesin. It is less certain, however, which other drugs can activate the alternate complement pathway.

We would like to report a severe reaction in a healthy 26-yr-old man undergoing cautery of nasal mucosa and catheterization of the right eustachean tube. There was no history of allergy other than nasal stuffiness which was aggravated by exposure to grass cuttings. More than 20 years ago he had been anaesthetized for the treatment of an upper limb fracture; details of the drugs used are not available, and he had not received anaesthesia on any other occasion.

The patient had an immediate histamine-mediated reaction causing profound and prolonged hypotension after gallamine 20 mg, thiopentone 450 mg and suxamethonium 125 mg i.v. Loss of circulating blood volume responded to the infusion of plasma and the vigorous application of conventional resuscitation measures. Serial blood samples showed massive conversion of complement C3 via the alternate pathway. Three hours after the start of the reaction 60% of the C3 complement had undergone conversion, which is greater than has ever been recorded after an Althesin reaction.

We conclude that gallamine, thiopentone and suxamethonium in combination, and perhaps individually, may trigger the alternate complement pathway in a susceptible individual, with life-threatening consequences.

David T. Brown
David Beamish
Edinburgh

REFERENCE

Watkins, J., Udnoon, S., Appleyard, T. N., and Thornton, J. A. (1976). Identification and quantification of hypersensitivity reactions to i.v. anaesthetic agents. *Br. J. Anaesth.*, **48**, 457.

AMETHOCAINE

Sir,—Dr Crawford mentioned the use of hyperbaric solutions of cinchocaine, lignocaine and prilocaine (Crawford, 1979). Many anaesthetists who have used amethocaine for spinal anaesthesia consider it to be superior to these drugs and would greatly value its availability in this country.

Why are drug companies reluctant to market a suitable preparation of amethocaine in Britain? Approaches to drug marketing concerns reap no harvest, and little explanation is given for this negative response. Could it be that the quantity used would be inadequate to justify the expensive and time-consuming process of reintroducing the drug? It seems so unsatisfactory that we should import disposable spinal anaesthesia sets from the U.S.A. with empty slots from which amethocaine ampoules have been removed! Amethocaine survives well the process of sterilization by autoclaving (Bridenbaugh and Moore, 1964). Ampoules containing the dry salt are particularly stable, and are readily mixed with dextrose solution to produce hyperbaric or hypobaric solutions suitable for subarachnoid administration.

R. W. Johnson
Bristol

REFERENCES

Crawford, J. S. (1979). Experience with spinal analgesia in a British obstetric unit. *Br. J. Anaesth.*, **51**, 431.
Bridenbaugh, L. D., and Moore, D. C. (1964). Does repeated heat sterilization of local anaesthetic drugs affect potency? *Anesthesiology*, **25**, 372.

INADVERTENT ADMINISTRATION OF 100% OXYGEN DURING ANAESTHESIA

Sir,—We read the correspondence on this subject with interest (Paymaster, 1978; Dodd, 1979) as we have also encountered similar difficulties with the Cape Waine Mk III anaesthetic machine.

On our machines the "emergency" oxygen switch is a push switch, spring-loaded, requiring a half turn to lock it into position. We have overcome the problem by requesting Cape Engineering Ltd to remove the mechanical stop. This ensures that the oxygen bypass cannot be left on inadvertently and thus solves the problem.

D. G. Larard
D. G. Tweedie
Warwick

REFERENCES

Dodd, K. W. (1979). Inadvertent administration of 100% oxygen during anaesthesia. *Br. J. Anaesth.*, **51**, 573.
Paymaster, N. J. (1978). Inadvertent administration of 100% oxygen during anaesthesia. *Br. J. Anaesth.*, **50**, 1268.

Br. J. Anaesth. (1979), **51**, 912

BOOK REVIEWS

Regional Anesthesia: Advances and Selected Topics. International Anesthesiology Clinics, Vol. 16, No. 4. Edited by Michael d'A. Stanton-Hicks. Published (1978) by Little, Brown and Company, Boston.

This issue of International Anesthesiology Clinics discusses, as its title implies, selected topics in the field of regional anaesthesia. There are eight articles, written by 12 international experts on the subject. The editor, Dr Stanton-Hicks, himself contributes the chapter on extradural blocks.

The book contains a wealth of excellent information, of a high academic standard, as would be expected from these authors, and much of it is very up-to-date. Unlike a textbook, it does not aim to provide a comprehensive view of the topic; nevertheless I believe that most practical anaesthetists in Great Britain would be led to expect from the title rather a different balance between scientific and clinical aspects. Four whole chapters cover pharmacology and pharmacokinetics, and the remaining four extradural, intercostal, sympathetic and upper arm (*sic*) blocks, respectively.

An editor has a difficult task to keep an eminent contributor within his own terms of reference and in the case of the first four chapters there is a lot of overlap. The first section (Dr Ben Covino), entitled Pharmacology of Newer Local Anesthetic Agents, inevitably contains a smattering of pharmacokinetics, biotransformation and placental transfer more fully dealt with in successive chapters. On the other hand, this chapter might very properly have included a discussion of the mode of action of local anaesthetic drugs.

The following excellent section, on "Pharmacokinetics and Biotransformation" (Drs Mather and Tucker), is logically presented and the basic principles are clearly described. Mathematical formulae are clearly expounded, but may be skipped by the non-mathematically minded reader without detriment to overall comprehension of the text. Some very interesting and useful data relating to the behaviour of lignocaine in i.v. regional anaesthesia are presented here, but not, alas, referred to in the index under i.v. regional anaesthesia.

Professor Löfström writes on tissue distribution with special reference to the lung, of which he gives us a very well-informed account. There is, however, inevitably, some repetition of the basic principles of pharmacokinetics.

An eminent triumvirate from Columbia University provides us with a section on uptake and effects of local anaesthetics in mother and fetus. There is some repetition of physiochemical properties and structural formulae, which, however, does not detract from the section, which enumerates with clarity some of the basic principles governing placental transfer of local anaesthetics.

The editor gives us the longest chapter, called "Clinical Uses of Epidural Anesthesia". It contains sections on Anatomy, Physiology and Pharmacology, Technique and Clinical Application. I was sorry to see that, despite 17 pages of indications, there was no systematic coverage of complications or contra-indications.

Both Dr Scott, on intercostal nerve blocks, and Dr Boas, on sympathetic blocks, make an excellent systemic approach to their subjects. The sections are lucid and well balanced and it is easy to find particular information within each.

The section entitled "Upper Arm Blocks" (? upper *limb* blocks) by Drs Nolte and Farrar contains some fascinating original research on the characteristics of nerve conduction blockade which one might have expected to find in the earlier scientific sections.

In summary, there is a wealth of information, both interesting and useful, to be found in this book, and my criticism stems only from the possibly too gentle hand of the editor in giving the excellent contributors too free a rein.

Felicity Reynolds

Advances in Neurology, Volume 20: Pathology of Cerebrospinal Microcirculation (eds J. Cervos-Navarro, E. Betz, G. Ebhardt, R. Serzt and R. Wullenweber). Published by Raven Press, New York. Illustrated.

This is another Conference Proceedings book under a thin disguise. The particular Conference was held in Berlin in September 1977, and included a number of leading authorities in the field. Given the basis of the book, it is natural that there is no uniformity of style or any development of themes. Topics of possible interest to anaesthetist readers include: microcirculatory failure during cerebral ischaemia, air embolism, blood–brain barrier changes with hypertension, c.b.f. measurements in severe head injury and cerebral artery spasm.

The book is expensive, although well produced, with many good illustrations. Those involved in neuroanaesthesia may wish to browse through a library copy to check on areas of particular interest.

D. G. McDowall

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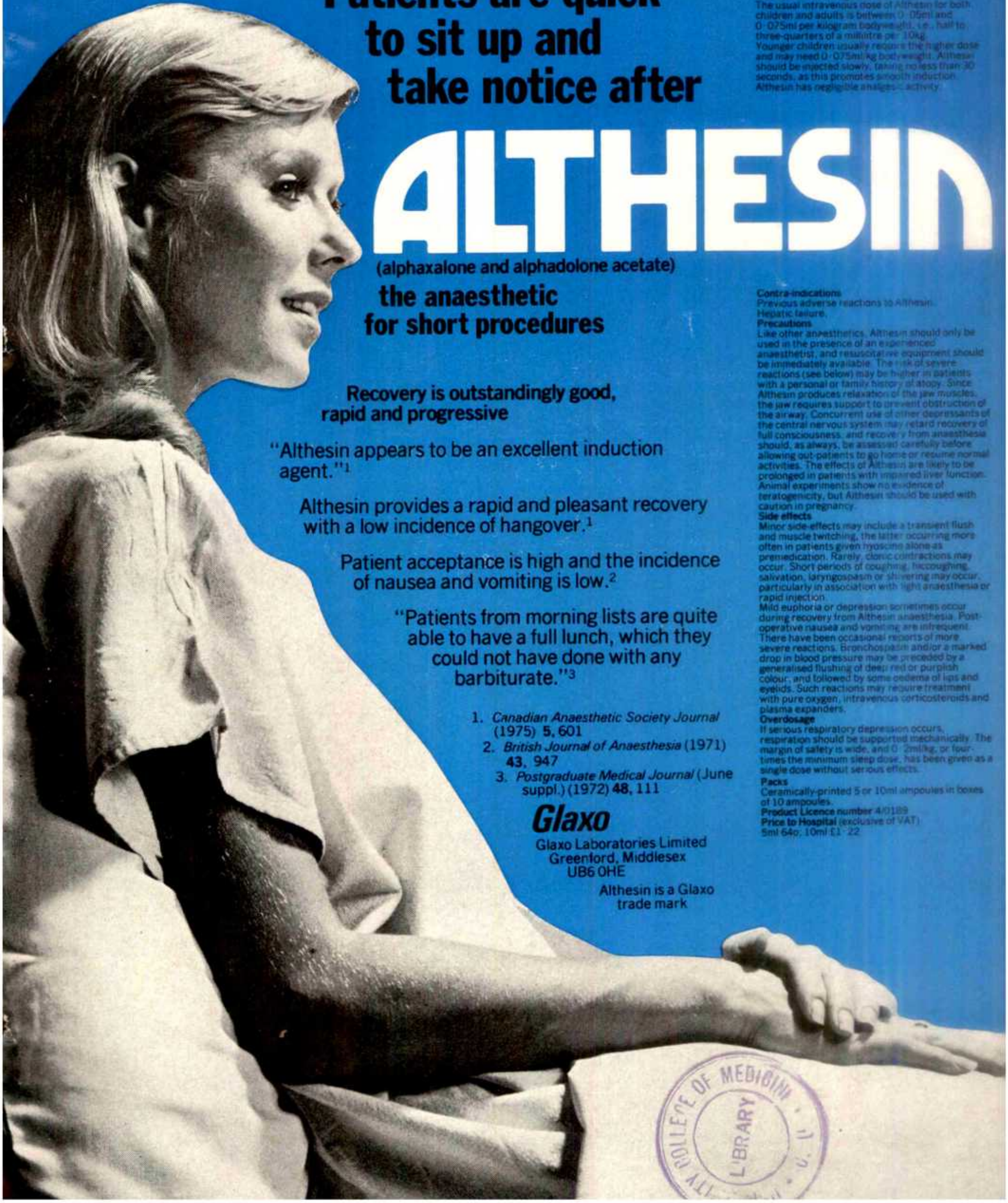

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1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
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Like other anaesthetics, Althesin should only be used in the presence of an experienced anaesthetist, and resuscitative equipment should be immediately available. The risk of severe reactions (see below) may be higher in patients with a personal or family history of atopy. Since Althesin produces relaxation of the jaw muscles, the jaw requires support to prevent obstruction of the airway. Concurrent use of other depressants of the central nervous system may retard recovery of full consciousness, and recovery from anaesthesia should, as always, be assessed carefully before allowing out-patients to go home or resume normal activities. The effects of Althesin are likely to be prolonged in patients with impaired liver function. Animal experiments show no evidence of teratogenicity, but Althesin should be used with caution in pregnancy.

Side effects

Minor side-effects may include a transient flush and muscle twitching, the latter occurring more often in patients given hyoscine alone as premedication. Rarely, clonic contractions may occur. Short periods of coughing, hiccoughing, salivation, laryngospasm or shivering may occur, particularly in association with light anaesthesia or rapid injection.
Mild euphoria or depression sometimes occur during recovery from Althesin anaesthesia. Post-operative nausea and vomiting are infrequent. There have been occasional reports of more severe reactions. Bronchospasm and/or a marked drop in blood pressure may be preceded by a generalised flushing of deep red or purplish colour, and followed by some oedema of lips and eyelids. Such reactions may require treatment with pure oxygen, intravenous corticosteroids and plasma expanders.

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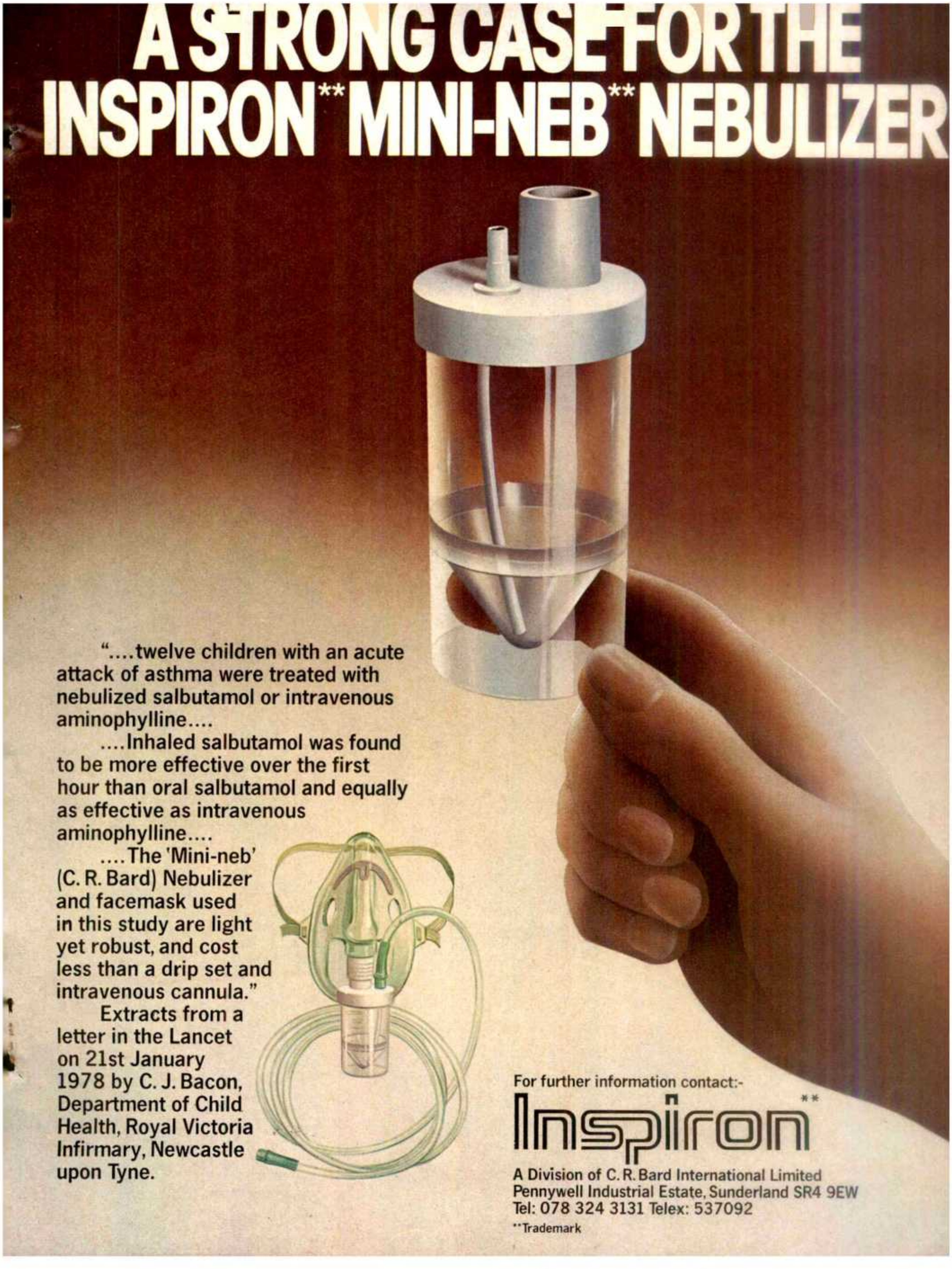

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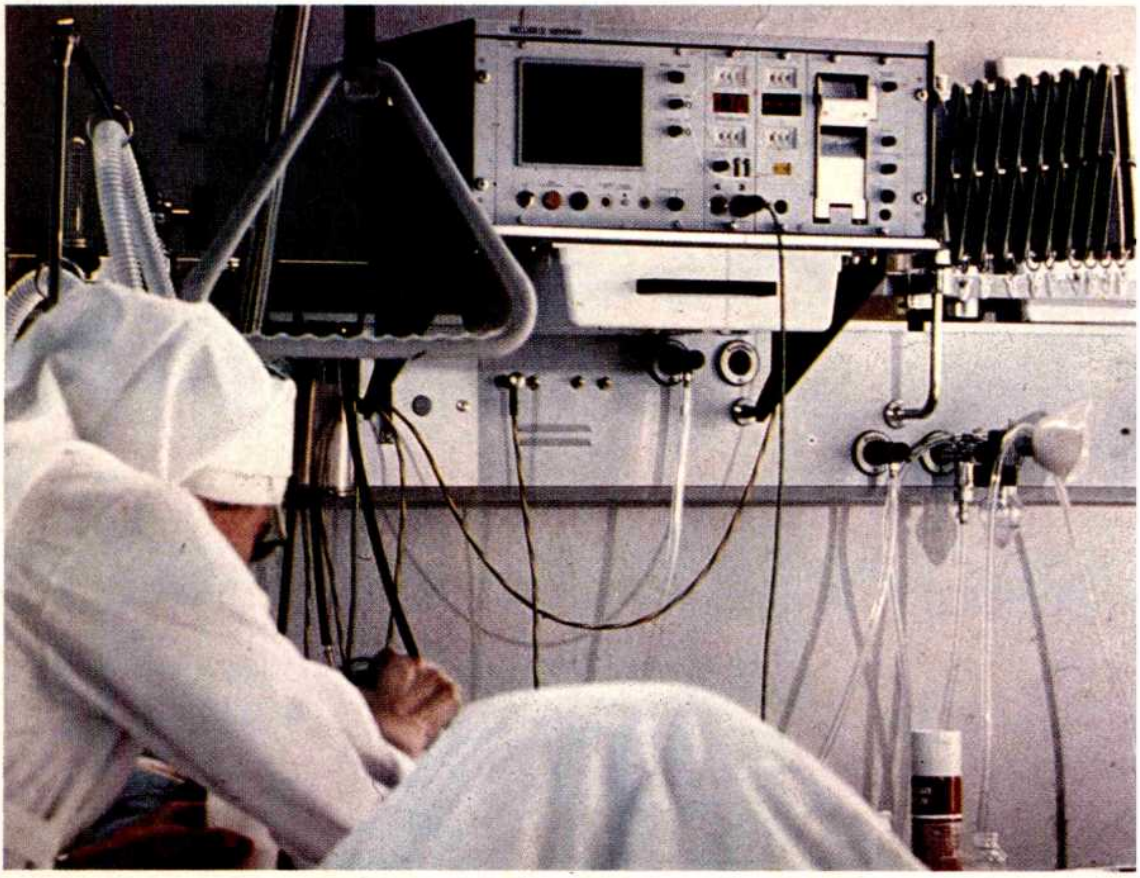

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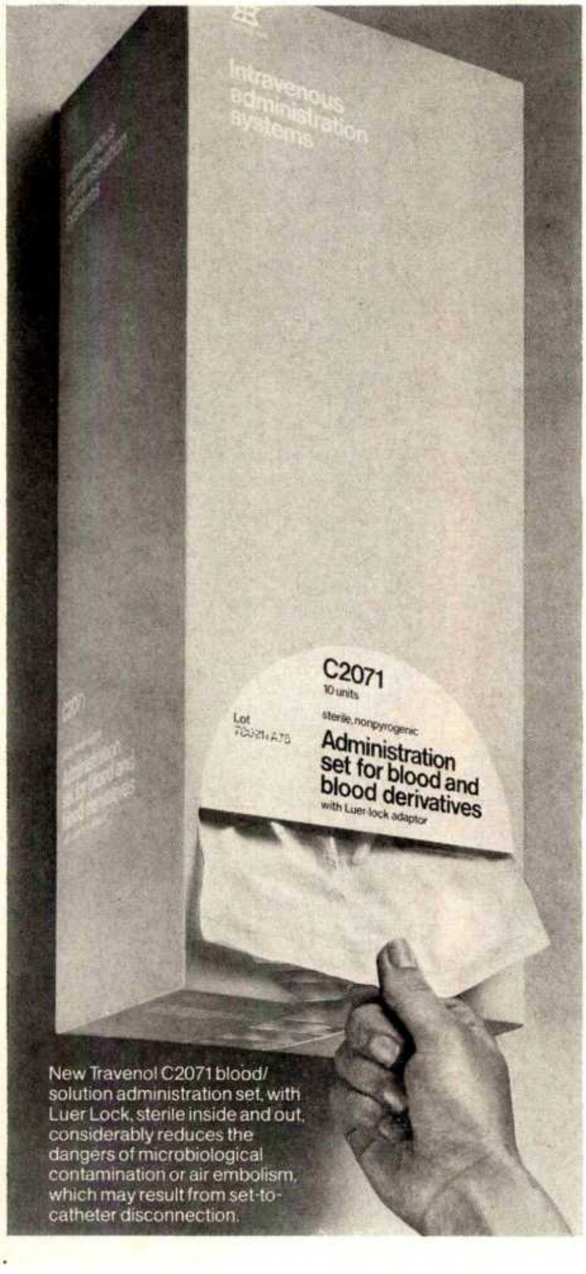
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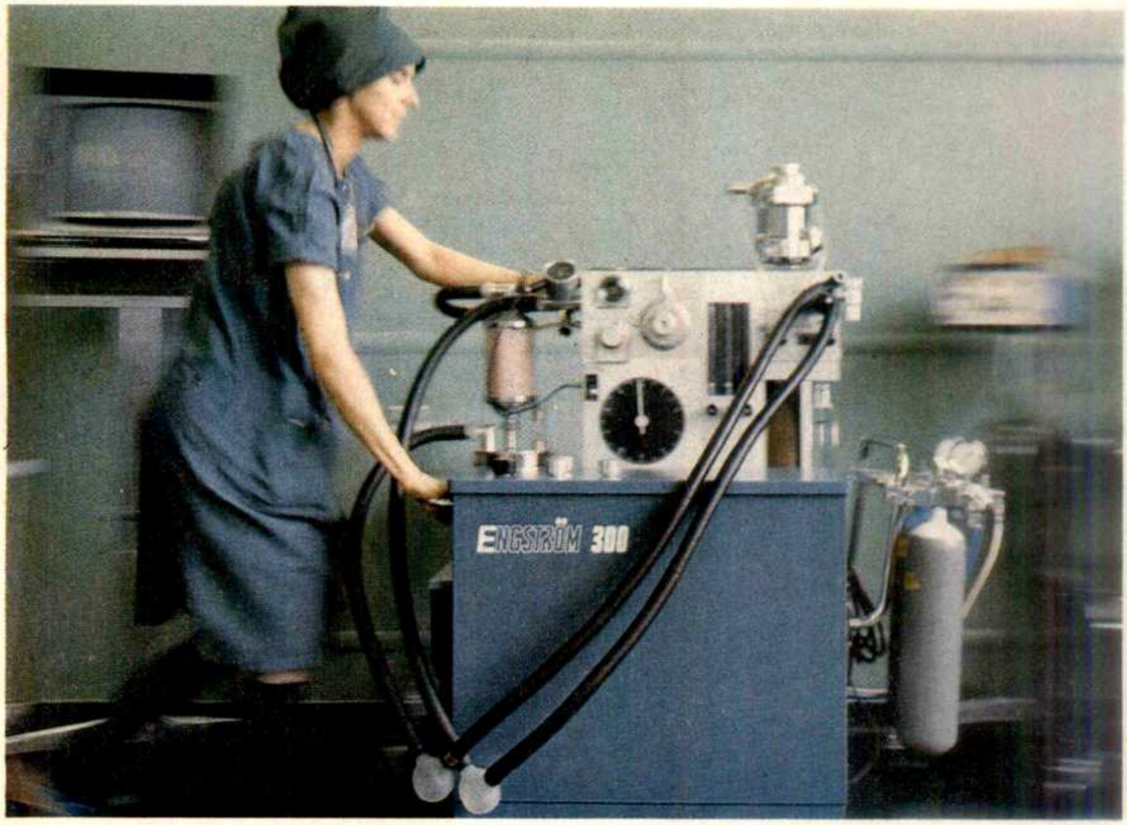

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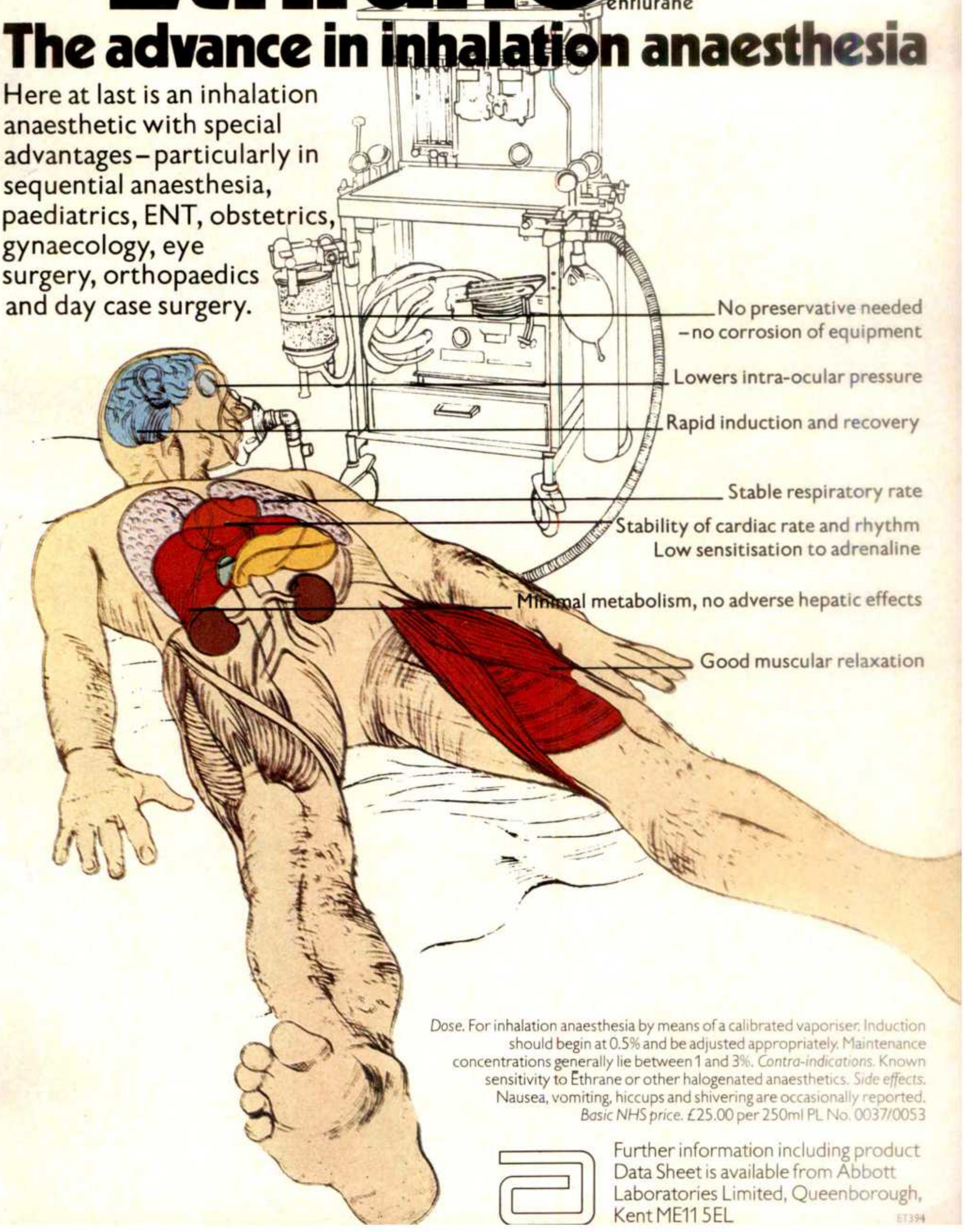

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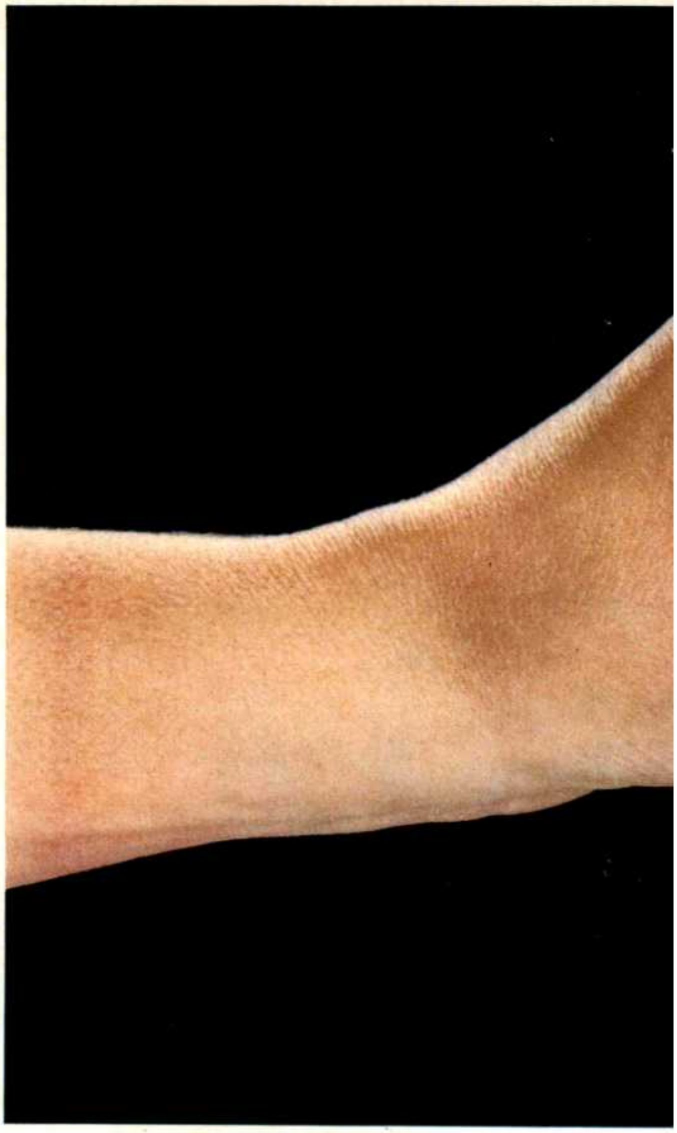

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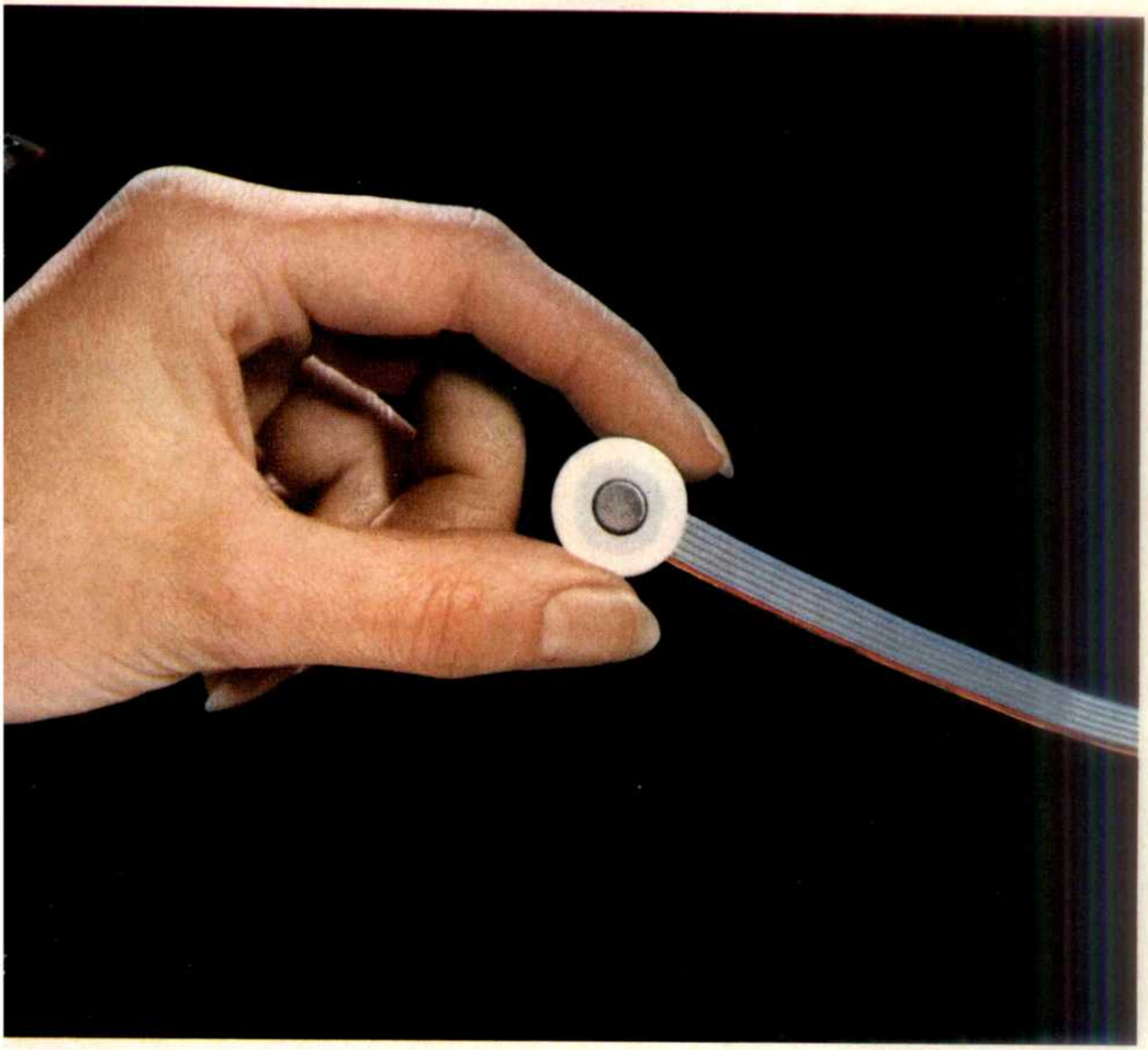

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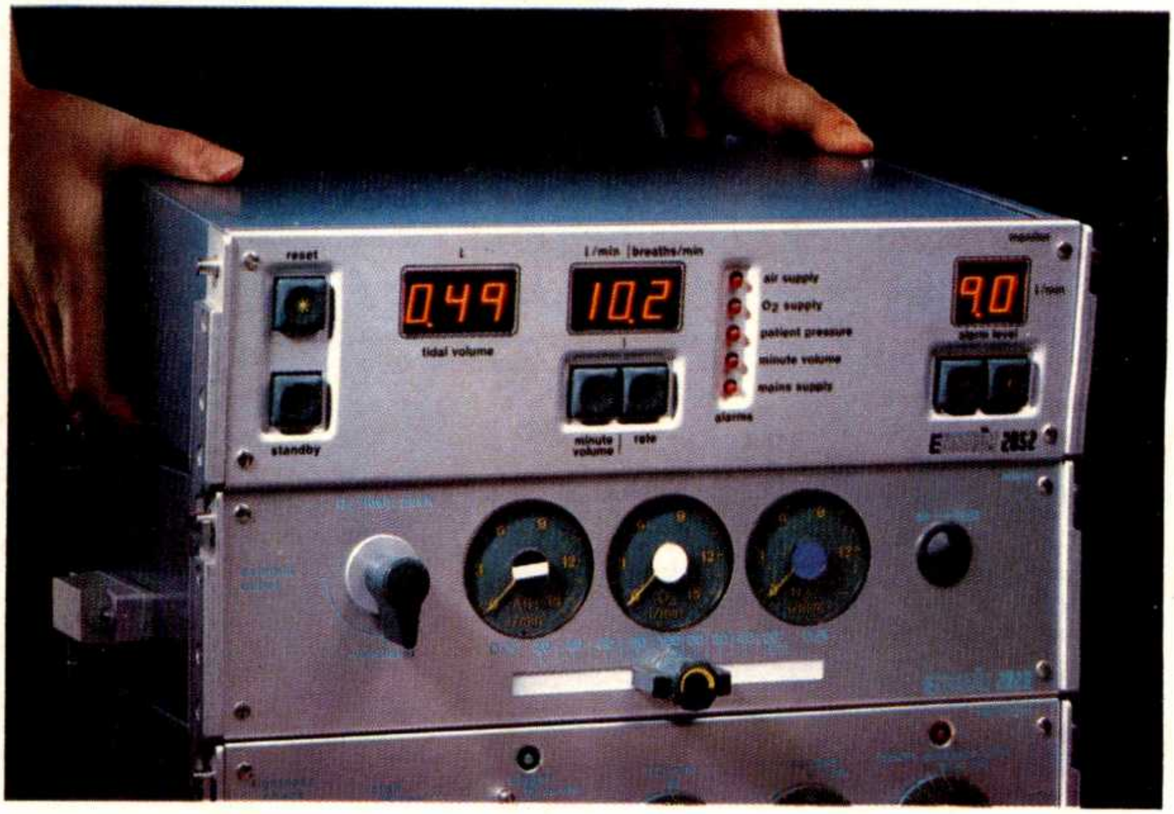

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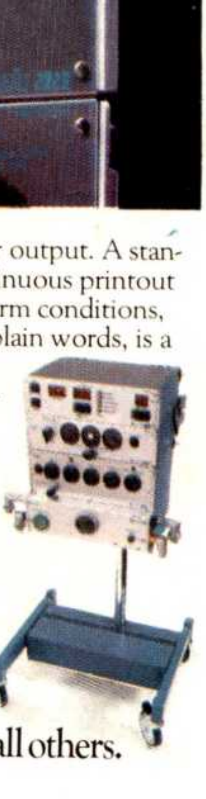

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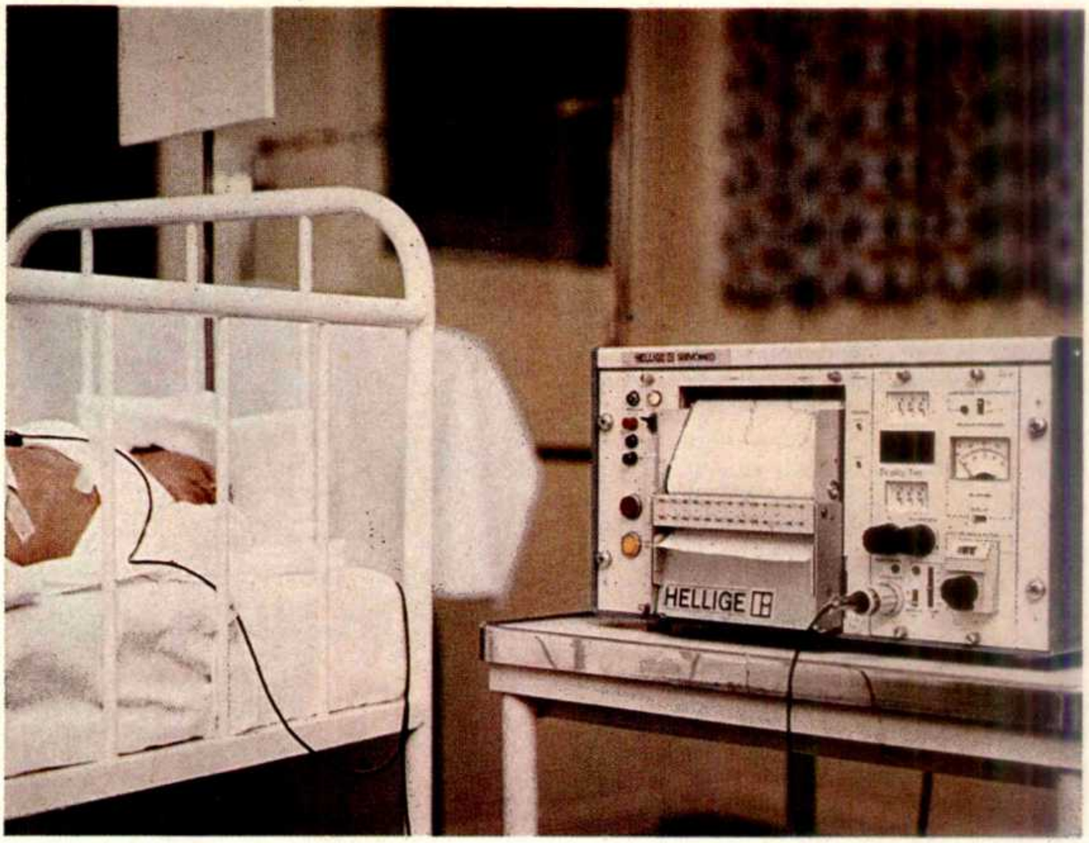

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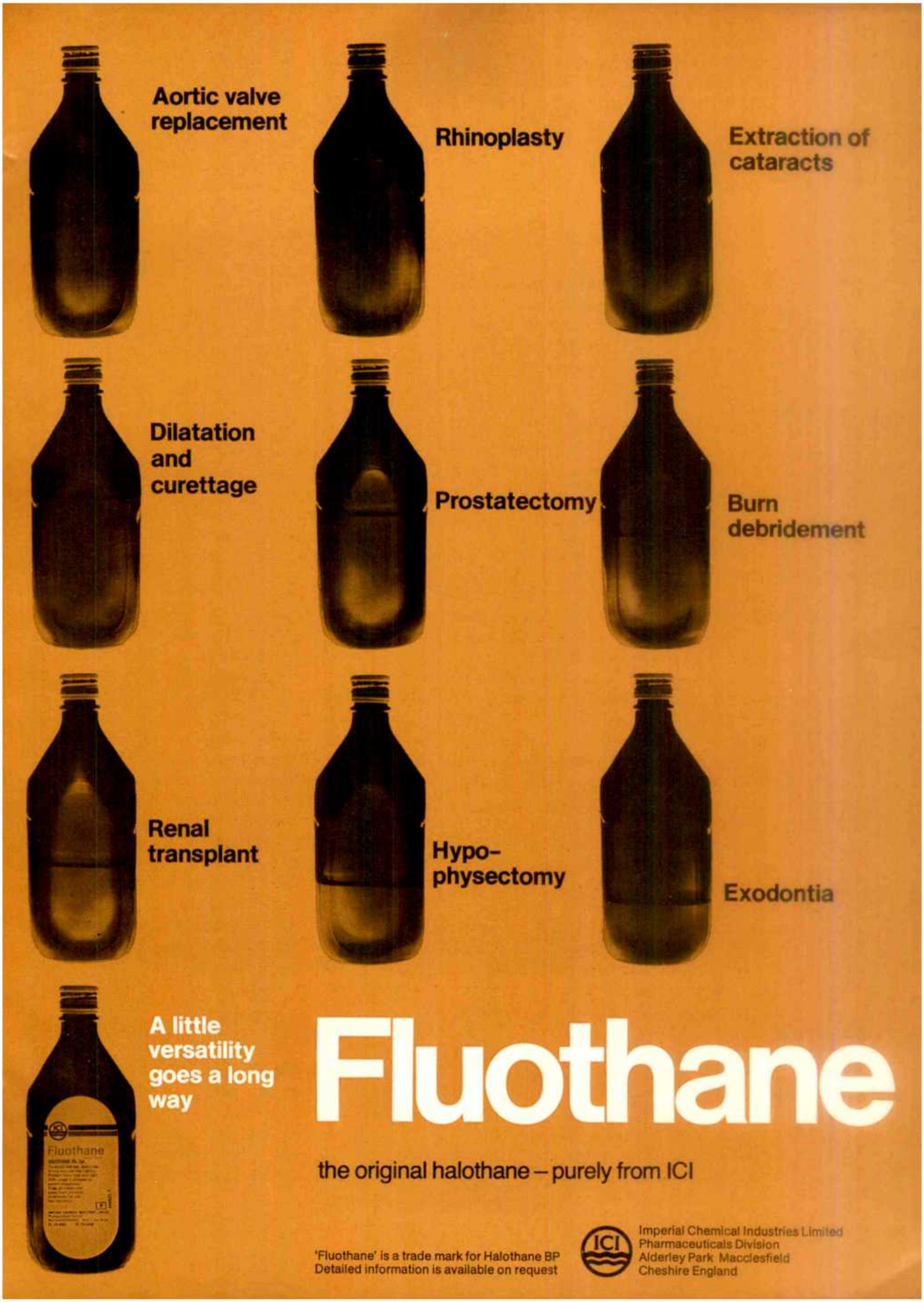

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Infant dosage: Intralipid 10% or 20%: 15–20 ml per kg body weight in 24 hours.

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Precautions: When daily intravenous fat administration for more than one week is indicated it must be ascertained, in order to prevent the development of cumulative lipaemia, that the patient is capable of eliminating the infused fat from the circulation, and this function can be tested in the following manner. In the morning following the first day's infusion, a citrated blood sample is drawn, preferably when the patient is still in a fasting state. The blood sample is centrifuged at 1,200–1,500 rpm. If the plasma is then strongly opalescent or milky, further infusion should be postponed. In the great majority of cases, plasma is completely clear 12 hours after the conclusion of an infusion of 2 g fat per kg body weight (corresponding to 20 ml of Intralipid 10% or 10 ml of Intralipid 20% per kg body weight). This test should be repeated at weekly intervals.

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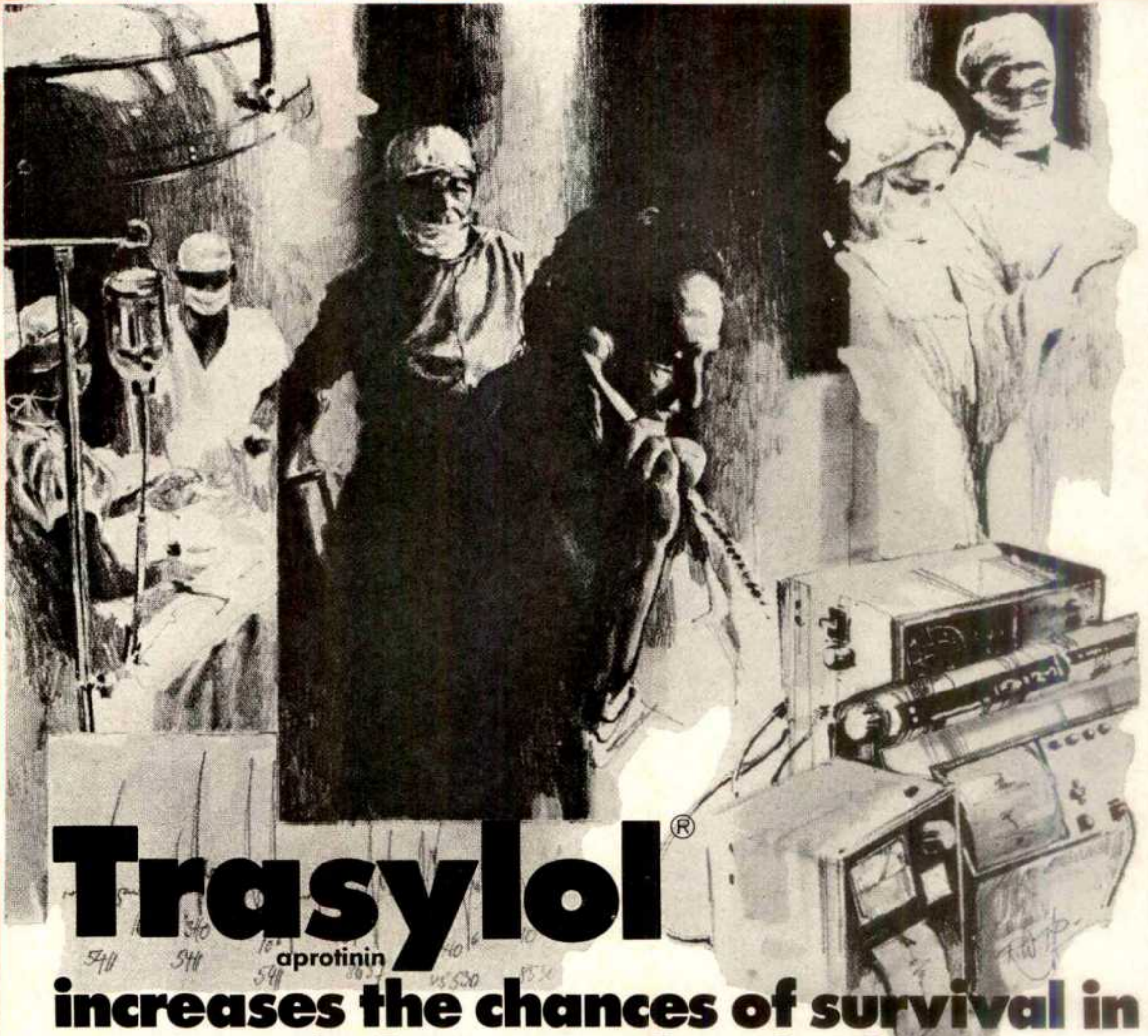

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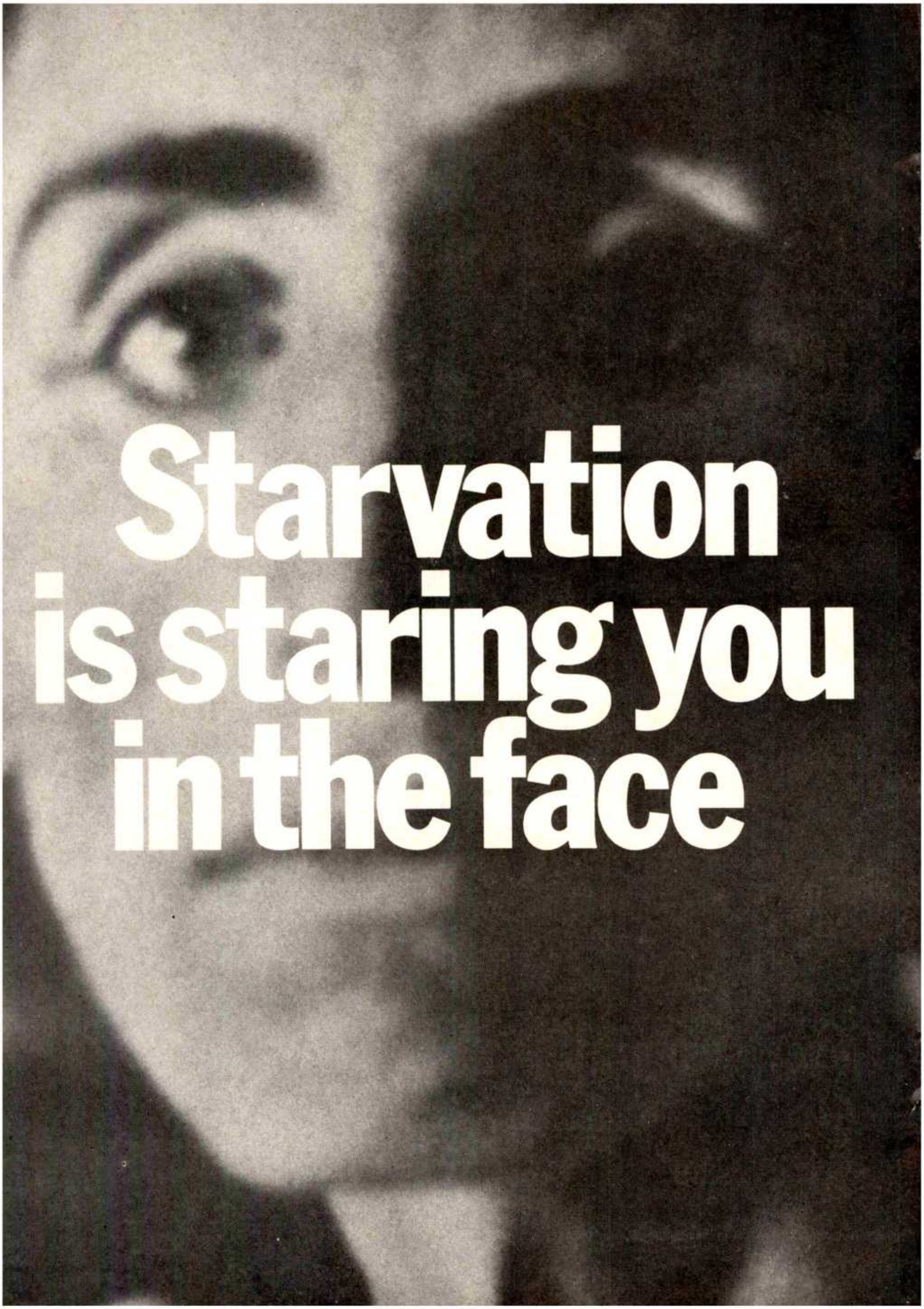
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Reference
1. Powell-Tuck, J., Farwell, J.A., Nielsen, T., and Lennard-Jones, J.E. (1978). Team approach to long-term intravenous feeding in patients with gastrointestinal disorders. Lancet, **ii,** 825-828.

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Der *Anaesthesist*

The organ of the
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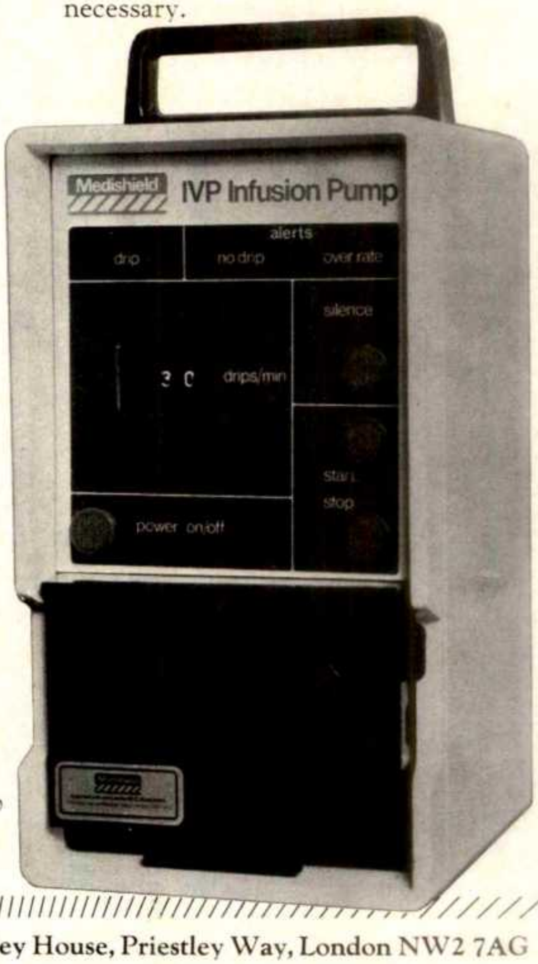

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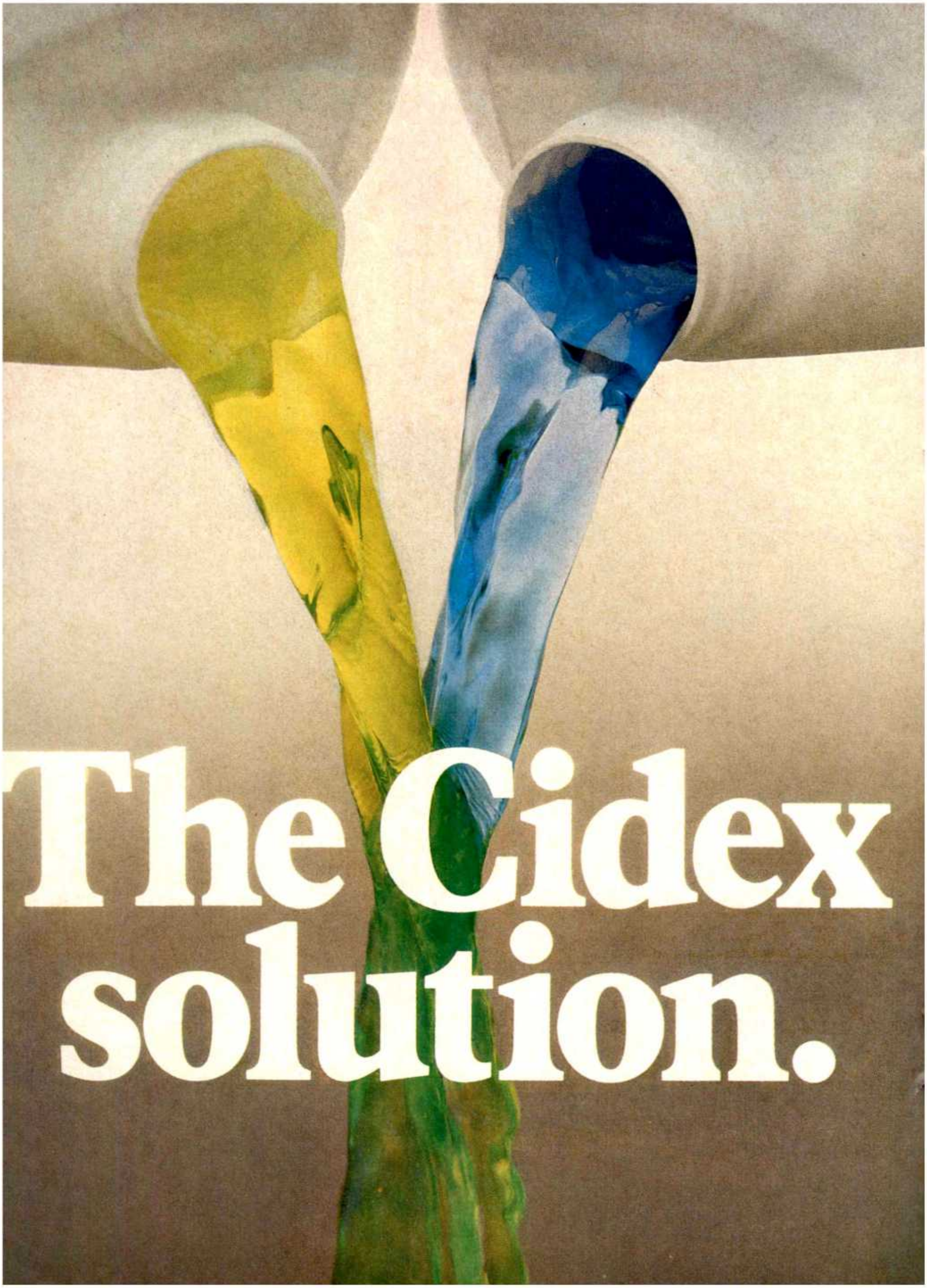
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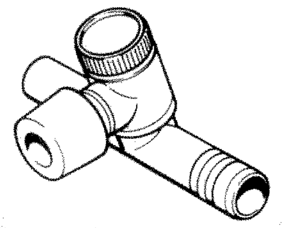

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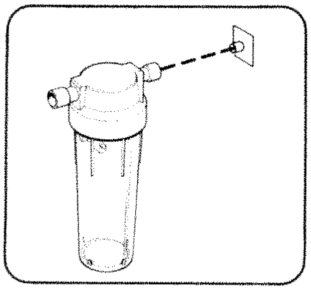

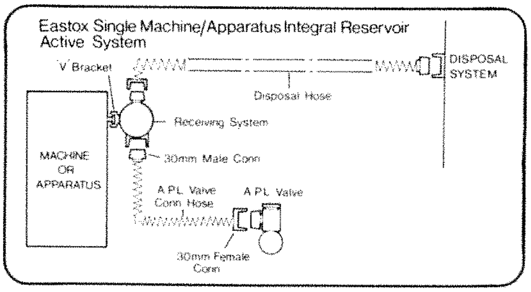

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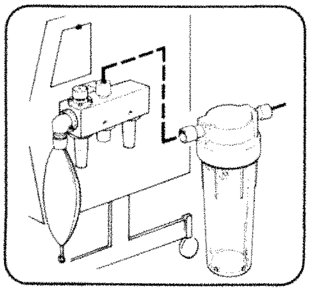

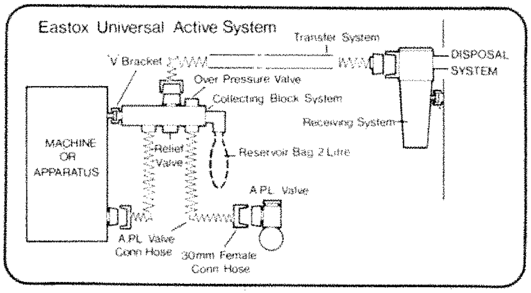

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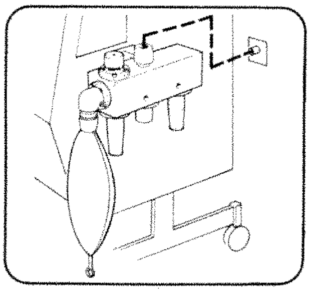

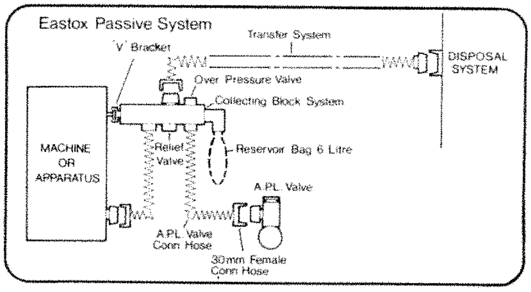

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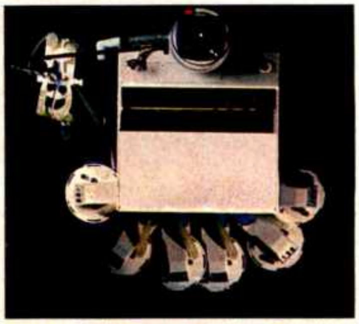

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 51, No. 10 OCTOBER 1979

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EDITORIAL

VIRAL HEPATITIS

Hepatitis may result from infection with a number of viruses, most commonly either virus hepatitis A (HAV) or virus hepatitis B (HBV); less commonly cytomegalovirus, herpes simplex virus or Epstein–Barr virus (infectious mononucleosis) may be responsible. These last infections may be encountered in patients receiving immunosuppressive therapy. Hepatitis A is endemic in all parts of the world. The infection is not normally transmitted by blood transfusion; although severe and sometimes fatal hepatitis may result, in most cases recovery is complete and there is no evidence of progression to chronic liver disease. In contrast, hepatitis B is commonly transmitted parenterally, and, in addition to occasionally causing fulminant hepatic failure, may be associated with the development of chronic liver disease. Some of those who survive infection with hepatitis B may become symptomless chronic carriers. Certain groups of patients are more likely to develop the chronic carrier state (Waterson, 1976) and these include patients with liver and kidney disease, a history of drug abuse, after tattooing, following acupuncture (Editorial, 1977) and persons coming from countries with a high endemic rate of infection. The carrier state may be quantified by the detection of various antigens in the serum (Zuckerman, 1979), and is characterized serologically by the finding of hepatitis B surface antigen (HBsAg, Australia antigen) and the absence of surface antibody. In some carriers hepatitis B DNA polymerase activity is present and another antigen, the *e* antigen, may also be detected. If both HBsAg and *e* antigens are present in the serum, this usually indicates a highly infectious individual.

The use of serological testing has now made possible the specific diagnosis of both hepatitis A and B. The application of such testing to the Blood Transfusion Service has dramatically reduced the risk of transfusion hepatitis. Indeed, it was assumed that such hepatitis could be almost entirely avoided. It has become clear, however, that transfusion hepatitis still occurs even in the absence of detectable infection with either virus A or B or other viruses which on occasion may cause hepatitis. The description non-A non-B hepatitis is now used for such occurrences, which are the major cause of transfusion hepatitis in North America. Non-A non-B hepatitis has been transmitted to chimpanzees (Alter et al., 1978); there is evidence that a carrier state exists and that in some patients chronic liver disease may occur. However, no specific laboratory tests are available for identifying non-A non-B hepatitis (Zuckerman, 1979).

The ability to diagnose virus hepatitis specifically in many instances is of relevance to anaesthetic practice in a number of respects. The risk of infection to anaesthetic personnel is obvious. There is epidemiological evidence of an increased frequency of liver dysfunction among anaesthetists (Spence and Knill-Jones, 1978) which may be partially, at least, accounted for by viral hepatitis. Simple measures are effective in preventing infection being transmitted from patients to staff (Waterson, 1976; Strunin, 1977). The first and obvious factor is awareness of the problem and this implies that patients should be screened for the presence of HBsAg and if possible *e* antigen; but even if these facilities are not available, patients in the high-risk categories should be regarded as antigen positive until it is proved otherwise. Since many cases of hepatitis follow accidental inoculation, present casual attitudes to the spillage of blood should be tempered with restraint. The wearing of gloves, a disposable gown and a mask, the use of disposable anaesthetic equipment where appropriate and safe disposal of such equipment afterwards, are obvious precautions. Hepatitis B virus is susceptible to heat, ethylene oxide and proprietary bleach solutions, such as Diversol BX (Diversey Ltd) which is a crystalline blend of chlorinated trisodium phosphate, admixed with a bromine salt. In solution, sodium hypochloride is formed, which reacts with the bromine to produce sodium hypobromite. This disinfectant is an example of the dual halogen type (chlorine and bromine).

Despite precautions the anaesthetist may find that he has inadvertantly inoculated himself with potentially infective material. What steps should be taken? First, it should be clearly established that the material was indeed infected. Second, the subject should have standard liver function tests performed and a test for the presence of hepatitis B surface antibodies. If these are present this implies that the individual has had a previous infection with hepatitis B and is now immune, and there is no risk of subsequent infection. In the event that such antibodies are not present and it is clear that infective material was inoculated, a dose of specific anti-HBs immunoglobulin should be administered. It should be noted that this form of immunoglobulin is recommended for the treatment of hepatitis B infection. Human normal immunoglobulin (gammaglobulin) is effective in preventing hepatitis A infection and is normally administered before visiting parts of the world where such infection is endemic. Human normal immunoglobulin is not effective in the treatment of hepatitis B infection, but it does appear to have a beneficial effect in preventing non-A non-B hepatitis (Editorial, 1978). Although specific anti-HBs immunoglobulin gives protection after inoculation accidents, clinical infection may be delayed beyond the normal incubation period of hepatitis B and individuals should be followed up for at least a year to be sure that they do not develop hepatitis. A more unusual use of specific anti-HBs immunoglobulin is during the anhepatic phase of liver transplantation in patients with hepatoma and who are antigen-positive. Four such patients have occurred in Britain and all remained free from the virus after surgery and one patient was still alive after 3 years (Johnson et al., 1978). Immunoglobulin confers only passive immunity and, except in the rare event of transplantation when the source of infection is removed, does not confer any long-term effect. Active immunity has been hampered by the inability to culture hepatitis B virus. Nevertheless, work is progressing toward the development of a vaccine which may be available soon.

Anxiety is often expressed by anaesthetists that, should they become chronic carriers of HBV, they may be at risk with regard to employment. This is not the case. There is, of course, a risk of chronic liver disease and incapacity. However, this is a rare event and, in most instances, the carrier state may be associated with only minimal evidence of liver dysfunction or may persist for only a relatively short period of time. The only bar to employment of HBsAg positive individuals is in the handling of blood products or employment in renal dialysis units. Indeed, an antigen-positive anaesthetist may be in great demand as the obvious choice to anaesthetize antigen-positive patients without risk.

Apart from personal hazard, what is the risk to the patient who either is incubating viral hepatitis or is a chronic carrier of hepatitis B when subjected to anaesthesia and surgery? The few studies of liver function in patients subjected to anaesthesia and surgery while incubating viral hepatitis or in the acute stages of the disease have suggested that liver function deteriorates subsequently (Harville and Summerskill, 1963; Hardy and Hughes, 1968; Marx et al., 1968). All anaesthetic techniques and many operative procedures will reduce liver blood flow. It seems sensible not to add additional problems to an already compromised liver. Therefore, where there is doubt, surgery should be delayed if possible. Such patients, however, are the minority and a far larger group are those who have already been diagnosed as chronic carriers of hepatitis B. Personal experience and the observations of others (Dykes, 1977) suggest that patients are not likely to undergo any "activation" of their virus infection as a result of anaesthesia and surgery and that any ill effects on the liver will be determined by the patient's state before operation. Clearly those with severe chronic liver disease are at risk if subjected to anaesthesia and major surgery.

The advent of specific serological diagnosis of viral hepatitis (Zuckerman, 1979) means that there is now additional help in determining the cause of jaundice after operation. Although, in most instances the cause of such jaundice is clear, on occasion liver dysfunction is unexplained and suspicion may fall on the anaesthetic used. The ability to determine if viral infection is involved may be an important factor if the patient requires further anaesthesia and surgery. In the majority of patients with unexplained postoperative jaundice or hepatitis it is now possible to eliminate viral hepatitis as the cause.

Leo Strunin

REFERENCES ON PAGE 926

Br. J. Anaesth. (1979), **51**, 915

EFFECT OF AN ACUTE INCREASE IN CEREBROSPINAL FLUID PRESSURE ON LUNG COMPLIANCE IN THE RABBIT

J. T. DAVIDSON, S. COTEV AND Y. FRENKIEL

SUMMARY

Cerebrospinal fluid pressure (P_{csf}) was increased acutely by the injection of normal saline into the cisterna magna of anaesthetized rabbits to values which interrupted cerebral blood flow. When increased P_{csf} was maintained for a minimum of 3 min, static lung compliance decreased and lung weight (after sacrifice) increased without marked change in arterial blood-gas tensions. The magnitude of the increase in P_{csf} did not affect the change in compliance and weight. There was marked unexplained metabolic acidosis. The pulmonary findings may result from a massive shift of blood from the systemic to the pulmonary circulation leading to increased permeability of the inter-endothelial junctions of the pulmonary capillaries.

It has been established both in clinical (Cameron, 1948; Ducker, 1968) and experimental (Bean and Beckman, 1969; Brasher and Ross, 1970) studies that a relationship exists between brain injury associated with increased intracranial pressure (i.c.p.) and acute respiratory insufficiency. While this relationship was noted first more than a century ago (Nothnagel, quoted by Benassi, 1937), there is controversy over the mechanism, particularly of neurogenic pulmonary oedema in which fulminant oedema with outpouring of protein-rich fluid from the respiratory tract occurs (Theodore and Robin, 1976). Moss and Stein (1976) postulate that the cardinal factor is hypoxic injury to the hypothalamus leading to an autonomically-mediated increase in pulmonary vein resistance and in capillary pressure. Other investigators were unable to demonstrate a neurally-mediated effect on the pulmonary circulation of an acute increase in i.c.p. (Valtonen, 1975; Jennett and North, 1976). It seems likely that the lung injury results from a massive, though evanescent, shift in blood volume from the systemic to the pulmonary circulation (Theodore and Robin, 1975).

We have developed a rabbit model in which i.c.p. is increased acutely by the injection of normal saline to the cisterna magna. We maintained the increase in i.c.p. for the minimum time necessary to produce consistent changes in lung compliance during controlled ventilation.

MATERIALS AND METHODS

The study was on 40 rabbits of either sex weighing 2–2.9 kg (mean 2.3 ± SD 0.038). Before induction of anaesthesia a blood sample was drawn from the central artery of the ear by percutaneous puncture. Any animal with abnormal blood-gas tensions was discarded. Following the induction of anaesthesia with sodium pentobarbitone 30 mg kg^{-1} i.v. tracheotomy was performed and a cuffed Magill tube (i.d. 3 mm) inserted to the trachea. Neuromuscular blockade was produced with gallamine 3 mg/kg body weight. The lungs were ventilated with room air using a constant volume pump respirator (Harvard 660) with tidal volume 12 ml/kg body weight and adjusting the frequency to maintain Pa_{CO_2} within the range 4.0–4.7 kPa. Once the ventilator had been set it was left unchanged during the course of the experiment. Normal body temperature was maintained with a heating pad. A femoral artery was exposed and a polyethylene catheter inserted and connected to a Statham P23 strain gauge. Thus the continuous recording of arterial pressure and sampling of arterial blood for gas analyses were possible.

The cisterna magna was cannulated by percutaneous puncture of the posterior atlanto-occipital membrane using a short-bevel 20-gauge needle, correct placement being indicated by a free flow of cerebrospinal fluid. Cerebrospinal fluid pressure (P_{csf}) was recorded using an additional Statham P23 strain gauge.

Transpulmonary pressure was measured with a differential pressure transducer (Sanborn 268B)

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connected to a (water-filled) length of polyethylene tube (PE260) passed through the mouth 19 ± 2 cm from the front teeth to reach the intrathoracic oesophagus (intrapleural pressure), and to a side arm from the tracheal tube.

The pulmonary pressure–volume curve was determined under static conditions by inflating the lungs with various volumes of air from a 100-ml syringe and recording the transpulmonary pressure (airway − oesophageal pressure) (Davidson et al., 1966). Compliance was calculated from the slope of the pressure–volume curve between functional residual capacity (FRC) and FRC + 40 ml.

After initial values had been recorded P_{csf} was increased rapidly by a manually regulated infusion of normal saline into the cisterna magna. The pressure was increased to between 200 and 300 mm Hg, and was maintained for 2–4 min. Based on P_{csf} and its duration, five experimental groups were studied (table I).

TABLE I. *Experimental groups*

Group	No. of animals in group	Cerebrospinal fluid pressure (mm Hg)	Duration of increase in c.s.f. pressure (min)
A	7	250	4
B	8	300	4
C	12	300	3
D	7	300	2
E	9	200	3

The mean volumes of saline (ml/kg body weight) necessary to increase and maintain P_{csf} for the stated times in the various groups are shown in table II.

TABLE II. *Volume of saline (ml/kg body weight) required to achieve and sustain the increase in* P_{csf}

Group	Mean volume	Range
A	20.6	13.2–29.1
B	33.4	16.7–61.0
C	20.8	8.2–41.9
D	13.2	8.0–20.7
E	20.7	11.4–30.3

In five anaesthetized control animals saline 40 ml/kg body weight was injected i.v. over a period of 4 min. In this group surgical procedures similar to those in the experimental groups had been undertaken, but P_{csf} was not increased (group F).

Initially, all measurements were made during the control period. They were repeated at 15, 30 and 60 min after the return of P_{csf} to control, and compared with the initial values by means of Wilcoxon's test for paired differences (one-tailed). At the end of the study the surviving animals were given a lethal dose of pentobarbitone and the lungs removed. The lung/body weight indices were determined by dividing the combined lung weight (× 100) by the body weight. The upper limit of normal in the rabbit is 0.45.

RESULTS

In four of five experimental groups (A, B, C and E) the increase in P_{csf} was maintained for a minimum of 3 min. In each of these there was a significant decrease in static lung compliance compared with the initial values, but the extent of the decrease did not differ significantly between the four groups. The decrease

TABLE III. *Static lung compliance differences (ml cm* H_2O^{-1}*) following increased* P_{csf}. **Calculated by means of Wilcoxon's test for paired differences (one-tailed). n.s. = not statistically significant*

	Group					
	A	B	C	D	E	F
15 min						
Mean diff.	2.6	1.94	2.3		2.22	
± SEM	0.79	0.49	0.47		0.44	
P*	< 0.02	< 0.01	< 0.005	n.s.	< 0.005	n.s.
30 min						
Mean diff.	2.67	2.01	1.96		2.28	
± SEM	0.79	0.47	0.41		0.45	
P*	< 0.02	< 0.01	< 0.005	n.s.	< 0.005	n.s.
60 min						
Mean diff.	2.53	1.74	1.8		2.29	
± SEM	0.79	0.49	0.37		0.6	
P*	< 0.02	< 0.01	< 0.005	n.s.	< 0.005	n.s.

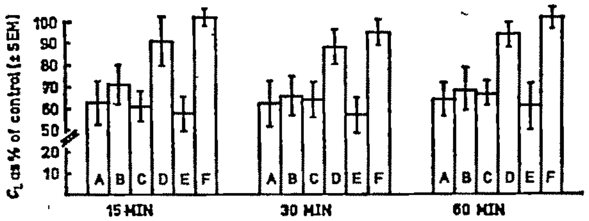

FIG. 1. Effect of increased P_{csf} on static lung compliance (C_L) (± SEM) in experimental and control groups.

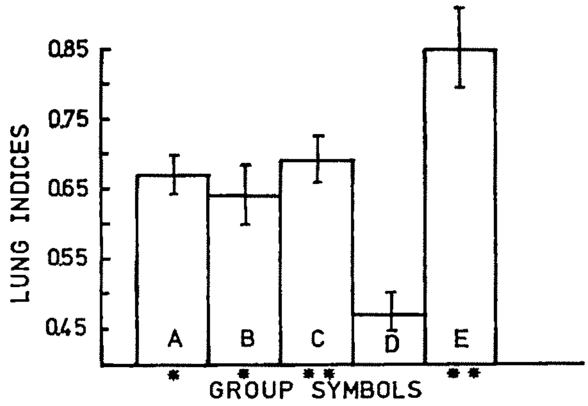

FIG. 2. Mean lung indices (± SEM) after exposure to an increase in P_{csf}. Wilcoxon's test for paired differences (one-tailed) showed significant increases in weight in groups A, B, C and E as compared with controls. $^*P < 0.05$; $^{**}P < 0.01$.

was detected 15 min after exposure of the animals to the increased P_{csf} and remained virtually unchanged during the remainder of the experimental period (fig. 1). In the fifth group (D) the increase in P_{csf} was sustained for only 2 min and in these animals the compliance was not decreased. No significant changes were noted in the control group (F) (table III). Figure 2 shows the indices of the excised lungs as an expression of lung weight, and it is clear that the decrease in compliance in groups A, B, C and E was paralleled by an increase in lung weight/body weight ratio. Only in group D was the lung index within normal limits for the rabbit.

Metabolic acidosis, which became more marked with time after the period of increase in i.c.p., was a constant finding (fig. 3). Every one of the 40 experimental animals studied developed an increase in base deficit and the animals in group D did not differ from the others. A typical tracing of the responses of the arterial pressure and heart rate to the increase in P_{csf} (Cushing response) (Cushing, 1902) is seen in figure 4. This figure records the increase in the transpulmonary pressure during the period of increased i.c.p., indicating a decrease in dynamic compliance. The arterial pressure peaked at very high values and returned to normal shortly after the return of P_{csf} to baseline. The percentage increases in systolic arterial pressure in the different groups were: A, 91%; B, 78%; C, 82%; D, 74%; E, 67%.

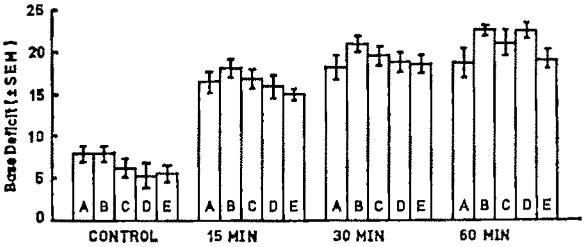

FIG. 3. Development of metabolic acidosis (base deficit mmol litre^{-1}) following exposure to an increase in P_{csf}.

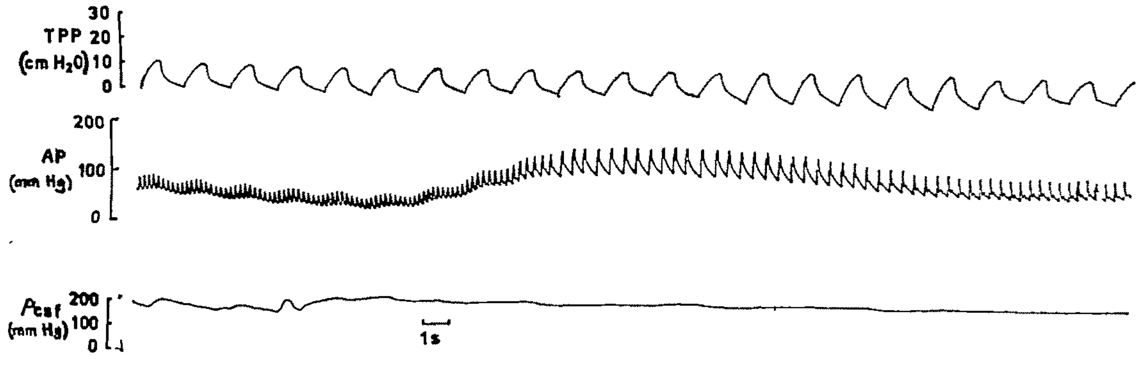

FIG. 4. Tracing from a rabbit showing the response of transpulmonary (TPP) and arterial (AP) pressure to acute changes in P_{csf}.

TABLE IV. *Arterial blood-gas tensions (mean ± SEM) following increased P_{csf} compared with the control group (F). Initial values were obtained after 15 min ventilation with room air*

Blood-gas tensions (kPa)	Group A	B	C	D	E	F
Initial values						
Pa_{O_2}	11.2 (±0.19)	11.4 (±0.28)	11.3 (±0.15)	11.3 (±0.23)	11.0 (±0.16)	11.0 (±0.23)
Pa_{CO_2}	4.0 (±0.2)	3.7 (±0.12)	4.0 (±0.09)	4.3 (±0.09)	4.4 (±0.17)	4.1 (±0.25)
15 min						
Pa_{O_2}	11.3 (±0.63)	11.7 (±1.24)	10.8 (±0.96)	13.0 (±0.32)	10.1 (±1.1)	11.2 (±0.21)
Pa_{CO_2}	3.6 (±0.29)	3.2 (±0.56)	3.7 (±0.19)	3.6 (±0.20)	4.0 (±0.23)	4.1 (±0.12)
30 min						
Pa_{O_2}	11.4 (±0.56)	11.8 (±1.33)	11.2 (±0.93)	13.0 (±0.53)	10.2 (±0.87)	11.0 (±0.37)
Pa_{CO_2}	3.6 (±0.25)	3.1 (±0.41)	3.6 (±0.2)	3.5 (±0.16)	3.6 (±0.2)	3.9 (±0.15)
60 min						
Pa_{O_2}	11.4 (±0.32)	12.0 (±1.5)	12.2 (±0.76)	13.3 (±0.37)	10.8 (±0.93)	11.0 (±0.59)
Pa_{CO_2}	3.3 (±0.27)	2.9 (±0.41)	3.1 (±0.24)	3.2 (±0.15)	3.6 (±0.23)	3.9 (±0.16)

The blood-gas tensions changed little in the course of the experiments. Minor alterations recorded did not follow a consistent pattern and only in group D was there a significant increase in Pa_{O_2} (table IV).

Figure 5 shows the static lung compliance and base excess in five control animals 1 h after the i.v. injection of normal saline 40 ml/kg body weight, and the indices of the excised lungs. These variables were essentially normal.

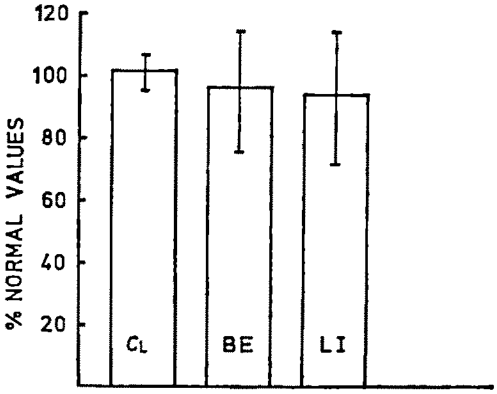

FIG. 5. Static compliance (C_L), base excess (BE) and lung index (LI) in control animals 1 h after i.v. injection of normal saline 40 ml/kg body weight.

DISCUSSION

In this study i.c.p. was increased by the injection of saline into the cisterna magna. With the increase in the pressure being transmitted freely throughout the cerebrospinal axis it would be expected to equilibrate throughout the entire subarachnoid and overlying extradural spaces (Langfitt et al., 1964). This hydrostatic method avoids problems, such as brain herniation, which may occur in experiments in which i.c.p. is increased by the inflation of a subdural balloon and which results in a supra- to infra-tentorial pressure gradient. In each experimental group the pressure developed within the subarachnoid space exceeded substantially the systolic arterial pressure, resulting in cessation of cerebral blood flow (Johnston et al., 1972; Hamer et al., 1973). The experimental model may be analogous to a clinical condition in which cerebral ischaemia is associated with temporary acute hypotension leading to zero perfusion pressure for several minutes, such as may occur following multiple trauma when head injury is associated with a decrease in cardiac output. However, it is recognized that no model of increased i.c.p. completely simulates clinical states. Within the limits of the study the variations in intracisternal pressure did not affect the results. In order to reach and maintain the increase in the intracisternal pressures the infusion of considerable volumes of fluid was necessary. Findings in the control group indicate that the changes recorded in the variables in this study did not result merely from volume infusion even when the latter was administered i.v.

The data from these *in vivo* experiments in rabbits demonstrate that an intense increase in i.c.p. of 3 min duration decreased static lung compliance and increased lung weight/body weight ratio. This further substantiates the findings of Beckman, Bean and Baslock (1971) who, in isolated lungs, found that severe mechanical head injury in the monkey caused a pronounced decrease in pulmonary distensibility. They attributed their finding to alteration in lung surfactants following sympathetic stimulation, and not to changes in the pulmonary parenchyma or airway blockage. In further studies Beckman, Bean and Baslock (1974) showed that stimulation of the stellate ganglion increased pulmonary surface tension and decreased lung compliance.

In contrast to those findings, the excised lungs of our experimental animals were significantly heavier than normal and, while the importance of intense sympathetic activity as a result of medullary and hypothalamic ischaemia during increased i.c.p. (Luisada, 1967) is recognized as the precursor of the changes, it seems likely that the essential factor is a sudden shift of blood from the systemic to the pulmonary circulation (Sarnoff and Sarnoff, 1952a, b). This leads to capillary damage and increased permeability in the low resistance system which persists even when the increase in i.c.p. and the pulmonary hypertension cease (Theodore and Robin, 1975). In the evolution of the concept of massive sympathetic discharge as a vital link in the pathophysiology of neurogenic pulmonary oedema, the work of Reynolds is pertinent. He showed that stimulation of the hypothalamic nuclei to produce irritation of the adjacent sympathetic pathways caused pulmonary oedema (Reynolds, 1963). MacKay (1950) demonstrated the protective effect of central nervous system depressants and adrenergic blocking agents, and this was later substantiated by Bean and Beckman (1969). We have noted previously that vascular changes induced by the injection of adrenaline in the rabbit may lead to pulmonary changes very similar to those described in the present work (Davidson and Charuzi, 1973). Shirley and colleagues (1957) used the term "stretched pore phenomenon" to describe the variability in the dimensions of the interendothelial junctions of the pulmonary capillaries and it has been demonstrated subsequently that an increase in hydrostatic pressure in these capillaries facilitates the movement of fluid and solutes from the circulation into the pulmonary interstitial space (Pietra et al., 1969; Szidon, Pietra and Fishman, 1972). This concept would explain our findings as regards both compliance and lung index.

Hypoxaemia is observed frequently in acute brain damage and Moss and his colleagues provided experimental support for their concept of an autonomically-mediated effect on the pulmonary vasculature which led to venular spasm, venous admixture and hypoxaemia (Moss and Staunton, 1971; Moss and Stein, 1976). In our study constant ventilation with room air was maintained, thus eliminating any possible effect of depression of the ventilatory response to carbon dioxide, and no impairment of gas exchange in the lungs was evident. Therefore we would agree with Jennett and North (1976) that there is no evidence for a specific deleterious effect of increased i.c.p. on gas exchange in the lungs.

At this stage we have no adequate explanation for the severe and progressive metabolic acidosis which developed in the presence of normal arterial blood-gas tensions. One can postulate that intense local vasoconstriction and tissue ischaemia continued after the initial "sympathetic storm". However, as arterial pressure returned to normal it would be necessary to assume an overall normal peripheral resistance, or changes in cardiac output in response to the altered peripheral resistance. It is hoped that further studies with our model will shed light on this problem.

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EFFET D'UNE AUGMENTATION AIGUE DE LA PRESSION DU LIQUIDE CEPHALO-RICHIDIEN SUR LA COMPLIANCE DES POUMONS CHEZ LE LAPIN

RESUME

La pression du liquide céphalo-rachidien (P_{csf}) a augmenté d'une manière aiguë, à la suite d'une injection saline normale dans la grande citerne de lapins anesthésiés, à des valeurs qui ont interrompu le débit sanguin cérébral. Lorsqu'on a maintenu une forte P_{csf} pendant un minimum de 3 min, la compliance statique des poumons a diminué et le poids des poumons (après sacrifice) a augmenté sans qu'il y ait eu de changements marqués dans les tensions sang-gaz artériels. L'importance de l'augmentation de la P_{csf} n'a pas affecté le changement dans la compliance et le poids. On a constaté une acidose métabolique marquée inexpliquée. Les observations pulmonaires peuvent découler d'un déplacement massif de sang allant de la circularion systémique à la circulation pulmonaire et entraînant une augmentation de la perméabilité des carrefours inter-endothéliaux des capillaires pulmonaires.

WIRKUNGEN EINES AKUTEN ANSTIEGES DES ZEREBROSPINALEN FLÜSSIGKEITSDRUCKES AUF DIE LUNGENDEHNBARKEIT BEIM KANINCHEN

ZUSAMMENFASSUNG

Der zerebrospinale Flüssigkeitsdruck (P_{csf}) wurde akut erhöht durch die Injektion einer normalen Salzlösung in die Cisterna magna von narkotisierten Kaninchen, und zwar auf Werte, durch die der zerebrale Blutfluss unterbrochen wurde. Wurde dieser erhöhte P_{csf} für mindestens 3 min aufrecht erhalten, sank die statische Lungendehnbarkeit ab, und das Lungengewicht stieg an, ohne dass es zu einem deutlichen Anstieg der Blutgasspannungen kam. Die Grössenordnung des Anstieges in P_{csf} beeinträchtigte die Veränderungen in Dehnbarkeit und Gewicht nicht. Es bestand deutliche, unerklärte metabolische Azidose. Diese pulmonaren Ergebnisse könnten das Ergebnis einer massiven Verlagerung von Blut aus dem systemischen in den pulmonaren Kreislauf sein, was zu einer erhöhten Permeabilität der interendothelialen Verbindungen der pulmonaren Kapillargefässe fürht.

EFECTO DEL AUMENTO AGUDO DE LA PRESION DEL FLUIDO CEREBROESPINAL EN LA ELASTICIDAD PULMONAR DEL CONEJO

SUMARIO

Al inyectar una solución salina normal en la cisterna magna de conejos anestesiados, se incrementó de manera aguda la presión del fluido cerebroespinal (P_{csf}) hasta valores que interrumpieron el flujo sanguíneo cerebral. Cuando se mantuvo durante un mínimo de 3 min la P_{csf} ampliada, la elasticidad estática de larga duración disminuyó y el peso del pulmón (después del beneficio) aumentó sin cambio notable en las tensiones arteriales sangre-gas. Hubo una significante acidosis metabólica inexplicada. Los hallazgos relacionados con los pulmones pueden ser el resultado de un traslado masivo de sangre de la circulación sistémica hacia la pulmonar, lo que resulta en un aumento de permeabilidad de las junciones inter-endoteliales de los capilares pulmonares.

Br. J. Anaesth. (1979), **51**, 921

INFLUENCE OF ANAESTHETIC AGENTS ON THE SURVIVAL OF RATS FOLLOWING ACUTE ISCHAEMIA OF THE BOWEL

P. H. BAVISTER AND D. E. LONGNECKER

SUMMARY

We compared the effects of ketamine and halothane anaesthesia on the survival of rats subjected to superior mesenteric artery occlusion. Survival was significantly greater with halothane. Animals anaesthetized with ketamine developed arterial hypocarbia during bowel ischaemic shock, while those receiving halothane did not. Arterial hypoxaemia was not present in either group. Haematocrits increased in both groups following bowel ischaemia. Excess lactate was increased significantly in non-survivors compared with survivors. The survival data contrast with previous results obtained after haemorrhagic hypotension and emphasize the need to consider differing therapeutic approaches in the various shock states.

Ketamine is recommended frequently in those poor-risk patients requiring surgery in whom poor cardiac function, hypovolaemia, hypotension or shock from any cause may complicate anaesthesia (Lippman and Cleveland, 1971; Bond and Davies, 1974; McGowan, 1975).

In rats subjected to haemorrhagic hypotension, Longnecker and Sturgill (1976) observed an improvement in survival and a decrease in the frequency of tissue hypoxia in the splanchnic organs of animals anaesthetized with ketamine compared with those receiving halothane, pentobarbitone or fluroxene. Maintenance of the blood flow to the splanchnic viscera in the animals anaesthetized with ketamine was suggested as a possible mechanism.

Since the various forms of shock are quite different from each other, the present study was designed to compare the effects of ketamine with those of halothane anaesthesia on the survival of rats subjected to shock as a result of superior mesenteric artery occlusion. This preparation is reported to be a model of the human with bowel ischaemic shock (Altura and Hershey, 1971).

METHODS

Thirty-two male Sprague–Dawley rats (body weight 367 ± 15 g, mean ± SEM) were anaesthetized with either ketamine (initial dose 125 mg kg^{-1} i.m. followed by doses of 30 mg kg^{-1} injected i.m. into alternate thighs, mean dose 1.67 ± 0.15 mg kg^{-1} min^{-1}) or halothane administered from a previously calibrated vaporizer (Fluotec Mk 3) at a concentration of 1.2% (v/v). All animals breathed 40% oxygen in air throughout the experiment. Rectal temperature was measured with a thermistor and was maintained at 36–37° C using an infra-red heat lamp. The left carotid artery was cannulated for recording mean arterial pressure (MAP) and for blood sampling.

The experimental programme consisted of a 60-min period during which baseline anaesthesia was established, 30 min of superior mesenteric artery (SMA) occlusion and a further 90 min of observation. Anaesthesia was discontinued a total of 120 min after the onset of SMA occlusion.

To produce SMA occlusion laparotomy was performed and two ligatures were tied around SMA to include a splint of polyethylene tubing. Occlusion of SMA was judged by pallor of the small bowel, loss of mesenteric arterial pulsation and a transient and small increase of MAP. The abdomen was closed with the splint protruding from the wound. Thirty minutes after the onset of occlusion the splint was removed to restore blood flow, which was judged by the systemic arterial hypotension which inevitably accompanied release of the occlusion. The number of animals surviving at 24-h intervals for the next 7 days was noted and cumulative survival rates were calculated.

MAP was recorded continuously and measured at 10-min intervals throughout the experiment except

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during the 10 min immediately following release of SMA, when MAP was measured each minute.

Arterial blood (2 ml) was sampled 10 min before occlusion of SMA and immediately before termination of the anaesthetic. Each sample was replaced by 6 ml of balanced salt solution (Polyonic, Cutter Labs) infused over 10 min.

Both blood samples were analysed immediately for pH, $P\text{co}_2$ and $P\text{o}_2$ (Radiometer BMS Mark III). Base excess was determined from a Siggaard-Andersen alignment nomogram and the haematocrit was measured in duplicate by the micro method. Aliquots of each sample were stored at 4 °C and lactate and pyruvate concentrations were determined later by an enzymatic method (Sigma Corporation). Excess lactate was calculated from the lactate/pyruvate values according to the method of Huckabee (1958). Distributive data (MAP, blood-gases, etc.) were analysed using Student's t test for paired or unpaired data. Survival rates were analysed by the Chi-square test using Yates' correction for small samples.

Four additional rats anaesthetized with ketamine were subjected to sham SMA occlusion to determine the effects of anaesthesia and operation on survival. The experimental procedure was identical to that described above except that SMA was isolated but not ligated in these animals.

RESULTS

The survival of both groups of animals at 24 h after SMA occlusion is shown in table I. Seven-day survival rates were identical to those at 24 h. More of the animals anaesthetized with halothane survived compared with those receiving ketamine ($P < 0.05$). The four sham operation animals survived for 7 days.

Figure 1 shows MAP for both groups of animals. Values for non-survivors and survivors were combined within each group since there were no significant differences between them. Control (time zero) was taken as the mean of the four values immediately before SMA occlusion. The figure shows the sudden decrease in MAP associated with SMA release followed by partial recovery and then a gradual decline which continued to the end of the period of measurement. MAP of the animals anaesthetized with ketamine was always greater than that of animals anaesthetized with halothane, and the reduction in arterial pressure immediately after release of the SMA occlusion was greater in those receiving ketamine.

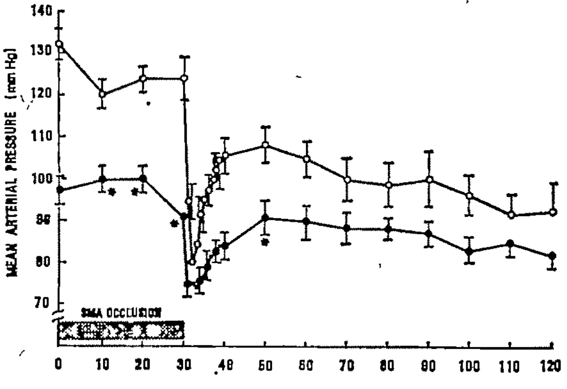

FIG. 1. Variation of mean arterial pressure (MAP) with time in rats subjected to superior mesenteric artery (SMA) occlusion during halothane (closed circles) and ketamine (open circles) anaesthesia. The control value (time zero) was averaged from MAP values obtained during the 30 min immediately before SMA occlusion. All values of MAP *except* those marked * were significantly different from control ($P < 0.05$).

A comparison of the blood chemical data (mean ± SEM) for halothane *v.* ketamine groups is shown in table II. Data for survivors and non-survivors within each group were not significantly different and were combined. Compared with those anaesthetized with halothane, animals receiving ketamine had significantly greater Pa_{O_2} and a slightly but significantly greater haematocrit before SMA occlusion. Ninety minutes after SMA release (control plus 120 min) rats anaesthetized with ketamine had a significantly smaller Pa_{CO_2}, greater Pa_{O_2}, more negative base

TABLE I. *Cumulative survival after SMA occlusion in rats anaesthetized with either halothane or ketamine. Survival rates were identical at 24 h and 7 days*

Halothane		Ketamine		Ketamine sham occlusion	
Survivors/ total	% Survival	Survivors/ total	% Survival	Survivors/ total	% Survival
10/16	62	3/16	19	4/4	100

TABLE II. *Arterial blood-gas tensions, haematocrits and excess lactates before and after SMA occlusion in rats anaesthetized with either halothane or ketamine (mean ± SEM); and significance of difference halothane* v. *ketamine*

	Halothane	Ketamine	Significance
H^+ (nmol litre^{-1})			
Control	56 ± 2	53 ± 1	n.s.
Control + 120 min	62 ± 2	57 ± 6	n.s.
P_{CO_2} (kPa)			
Control	7.6 ± 0.3	6.9 ± 0.2	n.s.
Control + 120 min	7.9 ± 0.6	4.7 ± 0.3	$P < 0.05$
P_{O_2} (kPa)			
Control	15.7 ± 1.0	19.1 ± 1.0	$P < 0.05$
Control + 120 min	15.5 ± 1.1	20.8 ± 0.9	$P < 0.05$
Base excess (mmol litre^{-1})			
Control	−4 ± 1	−4 ± 1	n.s.
Control + 120 min	−9 ± 1	−13 ± 1	$P < 0.05$
Haematocrit (%)			
Control	43 ± 1	47 ± 1	$P < 0.05$
Control + 120 min	48 ± 1	54 ± 1	$P < 0.05$
Excess lactate (mmol litre^{-1})			
Control + 120 min	0.7 ± 0.3	1.5 ± 0.3	n.s.

excess and greater haematocrit compared with those receiving halothane.

When all the data for survivors and non-survivors were pooled, excess lactate was significantly greater ($P < 0.01$) in non-survivors (1.5 ± 0.3 mmol litre^{-1}) compared with survivors (0.5 ± 0.3 mmol litre^{-1}).

DISCUSSION

The greater survival following SMA occlusion of the animals anaesthetized with halothane compared with those receiving ketamine is in marked contrast to the influence of the anaesthetic on the survival of rats subjected to haemorrhagic shock (ketamine greater survival than halothane (Longnecker and Sturgill, 1976)). Species and sex and the doses of the anaesthetic drugs were similar in the two studies, and the contrasting results probably reflect the differing pathophysiological effects of hypovolaemic *v.* bowel ischaemic shock. The dose of ketamine used was large compared with human requirements; however, it is a typical dose for the rat (McCarthy et al., 1965) and was identical to that used by Longnecker and Sturgill (1976) in their haemorrhage studies. The failure of ketamine to exert a beneficial effect in bowel ischaemic shock, despite its apparent benefits in haemorrhagic shock, is not unique to this drug. Galvin and Lefer (1978) studied the effects of dopamine in dogs subjected to bowel ischaemia and were able to demonstrate little or no therapeutic value for the drug despite its beneficial effects in haemorrhagic shock (Gifford et al., 1968).

The 100% 7-day survival of the four sham-operated animals suggests that the animals did not die as a result of the anaesthetic or operation alone. The probability of four consecutive survivors in animals receiving ketamine plus SMA occlusion (overall mortality 81%) is less than one in 700.

Excess lactate values were not significantly different between survivors and non-survivors within each anaesthetic group, although this value was increased significantly in all non-survivors as compared with all survivors when the data for all the shock rates were combined. Thus the view that excess lactate is an index of the severity of shock (Broder and Weil, 1964), can be sustained.

Although the decrease in MAP associated with the restoration of flow to the ischaemic bowel was relatively greater in animals receiving ketamine, the absolute values of MAP were consistently less in animals anaesthetized with halothane. Thus differences in MAP alone would not appear to explain the contrasting survival rates in the two groups.

The animals anaesthetized with halothane became hypercarbic, whereas those receiving ketamine hyperventilated in response to the bowel ischaemia. The results are consistent with a previous study which demonstrated that halothane, but not ketamine, depressed the ventilatory response to haemorrhagic hypotension (Longnecker, McCoy and Drucker, 1979).

Arterial haematocrit values were slightly, but significantly, greater in animals receiving ketamine compared with those receiving halothane. Although the control values were significantly different, the biological significance of this small difference (43% *v.* 47%) seems minimal. Both groups developed an increase in haematocrit following release of SMA occlusion. Either an increase in red blood cell mass or a decrease in plasma volume could account for these changes, although a loss of plasma volume into the ischaemic bowel would appear to be the most likely explanation. Neither Milliken, Nahor and Fine (1965) nor Altura, Hershey and Mazzia (1966) were able to alter the survival rates of animals subjected to bowel ischaemic shock by the replacement of plasma volume alone. Therefore, it is unlikely that the differences in survival could be explained by differences in circulating volume.

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INFLUENCE DES AGENTS ANESTHESIANTS SUR LA SURVIVANCE DES RATS APRES UNE ISCHEMIE AIGUE DES INTESTINS

RESUME

Nous avons comparé les effets d'une anesthésie à la kétamine et à l'halothane sur la survivance des rats soumis à une occlusion de l'artère mésentérique supérieure. La survivance a été infiniment plus grande avec l'halothane. Les animaux anesthésiés à la kétamine ont développé une hypocarbie artérielle pendant le choc ischémique de l'intestin, alors que cela n'a pas été le cas avec ceux auxquels on avait administré de l'halothane. Il n'y a eu aucune hypoxémie artérielle dans l'un ou l'autre cas. Le nombre des hématocrites a augmenté dans les deux groupes pendant l'ischémie des intestins. L'excédent de lactate a augmenté d'une manière significative chez ceux qui n'ont pas survécu par rapport à ceux qui ont survécu. Les connées relatives à la survivance contrastent avec les résultats obtenus précédemment après hypotension hémorragique et font qu'il est essentiel d'envisager des thérapeutiques différentes pour les divers états de choc.

EINFLUSS VON NARKOSEMITTELN AUF DAS ÜBERLEBEN VON RATTEN NACH AKUTER EINGEWEIDE-ISCHÄMIE

ZUSAMMENFASSUNG

Wir verglichen die Wirkungen von Ketamin- und von Halothannarkose auf das Überleben von Ratten nach Hervorrufung von Okklusion der Mesenterialarterie. Die Überlebensrate war mit Halothan wesentlich höher. Mit Ketamin narkotisierte Tiere entwickelten während des ischämischen Schocks der Eingeweide arterielle Hypokarbie, was bei den mit Halothan narkotisierten nicht der Fall war. Arterielle Hypoxamie trat in keiner Gruppe auf. Hämatokriten stiegen während Eingeweide-Ischämie in beiden Gruppen an. Laktatüberschuss stieg in den Nicht-Überlebenden im Gegensatz zu den Überlebenden stark an. Die Überlebensdaten widersprechen früheren Resultaten, die nach hämorrhagischer Hypotension erzielt worden waren, und betonen die Notwendigkeit für andersartige therapeutische Methoden in den verschiedenen Stadien von Schock.

INFLUENCIA DE LOS AGENTES ANESTETICOS EN LA SUPERVIVENCIA DE RATONES DESPUES DE ISQUEMIA INTESTINAL

SUMARIO

Comparamos los efectos de la anestesia por quetamina y por halotano en la supervivencia de ratones sometidos a una

oclusión de la arteria mesentérica superior. La supervivencia fue mucho mayor con el halotano. Los animales anestesiados con la quetamina padecieron de hipocarbia arterial durante el choque isquémico intestinal, mientras que no la hubo en los que recibieron halotano. No hubo hipoxemia en ninguno de los dos grupos. En ambos, aumentaron los hematocritos durante la isquemia intestinal. El exceso de lactato aumentó de manera significante en los animales que no sobrevivieron en comparación con los sobrevivientes. Los datos sobre supervivencia están en contraste con los resultados previos obtenidos después de hipotensión hemorrágica y enfatizan la necesidad de considerar enfoques terapeúticos distintos en los varios estados de choque.

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ACUTE EFFECT OF FENTANYL ON HAEMODYNAMICS AND MYOCARDIAL CARBOHYDRATE UTILIZATION AND PHOSPHATE RELEASE DURING ISCHAEMIA

G. J. VAN DER VUSSE, H. VAN BELLE, W. VAN GERVEN, R. KRUGER AND R. S. RENEMAN

SUMMARY

The effect of fentanyl 25 μg/kg body weight i.v. on left ventricular haemodynamics, myocardial carbohydrate utilization and phosphate release during ischaemia in dogs was investigated. A reproducible degree of ischaemia could be obtained by partial occlusion (stenosis) of the interventricular artery, using an inflatable cuff. Inducing stenosis twice made it possible to use the animal as its own control. Arterio–local venous differences of glucose increased during ischaemia and lactate and inorganic phosphate were released from the ischaemic myocardium. Fentanyl administered before the second stenosis reduced heart rate and, to a lesser extent, mean aortic pressure and left ventricular d*P*/d*t* max. The release of lactate and inorganic phosphate was diminished during the period of ischaemia. These findings suggest that fentanyl prevents excessive breakdown of energy-rich phosphates and high anaerobic production rate of lactate by decreasing the energy demand of the ischaemic myocardium.

Ischaemic heart disease is commonly caused by an obstruction of one or more coronary arteries. Tissue hypoxia leads to anaerobic lactate formation and, in severe ischaemia, aerobic energy production is almost completely replaced by anaerobic energy supply. Breakdown of creatine phosphate and ATP results in a shortage of energy-rich phosphates for adequate muscle contraction (Opie, 1976). Cellular accumulation of carbon dioxide, lactate and inorganic phosphate occurs and produces acidosis which may contribute to cellular damage.

To diminish the chance of myocardial acidosis occurring during anaesthesia in patients with coronary artery disease, the drugs used should preferably decrease the oxygen demand of the ischaemic myocardium. Fentanyl has been reported to decrease the oxygen demand of the left ventricle (Freye, 1974; Kettler and Sonntag, 1974; Patschke, Gethmann et al., 1976; Patschke, Hesse et al., 1976) and to suppress the responses to stress (Florence, 1978; Hall, 1978).

The present investigation was designed to study in detail the effects of fentanyl on myocardial ischaemia. The influence of this drug on myocardial carbohydrate metabolism and inorganic phosphate release was investigated in dogs with a standardized stenosis of a coronary artery. A preliminary abstract of this study has been published elsewhere (Reneman et al., 1977).

MATERIALS AND METHODS

Experiments were performed on mongrel dogs of either sex and unknown age (weight 22–30 kg). The animals were premedicated with Hypnorm (1 ml/kg body weight i.m.) as described by Marsboom and others (1964). Anaesthesia was induced with sodium pentobarbitone (10 mg/kg body weight i.v.) and, after tracheal intubation, was maintained with nitrous oxide in oxygen. Pulmonary ventilation was kept constant, during the experiments, with a positive-pressure respirator (Bird).

The e.c.g. was derived from limb leads. The chest was incised through the left fifth intercostal space and the pericardium opened over the antero-lateral aspect of the heart. Ascending aortic pressure was measured via the femoral artery with a polyethylene catheter connected to a pressure transducer (Telco). The pressure in the interventricular artery distal to the site of stenosis was measured through a small side branch (van der Meer and Reneman, 1972) with a polyethylene catheter (P.E. 50, Clay Adams) connected to a pressure transducer (Telco). The length and diameter of the catheters for aortic and coronary artery pressure measurements were such that no difference in delay could be detected between the measuring systems. Left ventricular pressure was measured through the

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left brachial artery with a catheter-tip micro manometer (Millar) and its maximal first derivative dP/dt max was determined with an analog differentiator (Schaper, Lewi and Jageneau, 1965). The frequency response of the differentiator was 100 Hz (3 dB). The haemodynamic variables were recorded continuously using a multichannel Schwarzer recorder. Heparin 5000 i.u. was administered i.v. to keep patent the catheters used for pressure measurement.

An inflatable cuff was placed on the interventricular artery just distal to the diagonal branch. The cuff was connected through silastic tubing to a micrometer. The system was filled with distilled water so that the cuff could be inflated carefully until the desired degree of stenosis—mean coronary artery pressure of approximately 15–30 mm Hg—was reached. This range of pressures was selected since preliminary experiments had shown that lactate production occurred consistently at this degree of stenosis.

Arterial blood was sampled through the catheter used for aortic pressure measurement. Local venous blood samples were obtained through a polyethylene catheter (P.E. 60, Clay Adams) inserted into the interventricular vein by the Seldinger technique. The tip of the catheter was placed halfway between the site of stenosis and the apex, being approximately the site of maximum ischaemia (Jageneau et al., 1975). All blood samples were immediately deproteinized with cold perchloric acid and analysed using automated techniques for lactate (Apstein, Puchner and Brachfeld, 1970), inorganic phosphate (van Belle, 1970) and glucose.

After a recorded control period, the cuff was inflated to the desired degree of stenosis and was kept inflated for a period of 15 min. Then the cuff was deflated for approximately 30 min. After this period of stabilization, a second stenosis similar to the first was applied. In both procedures, arterial and venous blood samples were taken 10 min before, just before and usually 5, 10 and 15 min after the stenosis was induced. Haemodynamic variables were calculated at these times (−10, 0, 5, 10, 15, 35, 45, 50, 55 and 60 min).

The animals were allocated to four groups. In group I control experiments were performed without constant heart rate ($n = 10$). In group II fentanyl 25 µg/kg body weight (Janssen, Niemegeers and Dony, 1963) was injected i.v. approximately 5 min before induction of the second stenosis ($n = 10$). In group III bipolar stimulation electrodes were sutured to the right ventricle. In these experiments ($n = 10$), heart rate was kept constant at 140 beat min^{-1} with a programmable stimulator (Geivers et al., 1973). In group IV heart rate was kept constant as in group III and fentanyl 25 µg kg^{-1} was injected i.v. 5 min before the second stenosis ($n = 6$).

Data analysis

Applying the same degree of stenosis twice makes it possible to use each animal as its own control. To study the effect of stenosis, the values of haemodynamic and biochemical measurements during each stenosis (5, 10 and 15 min and 50, 55, 60 min) were compared with those just before induction of the stenosis (0 and 45 min). By comparing the values of the determined variables during the first (5, 10 and 15 min) and the second stenosis (50, 55 and 60 min) information can be obtained on the reproducibility of the changes induced by a stenosis of comparable severity (groups I and III) and on the effect of fentanyl during ischaemia (groups II and IV). The effect of fentanyl on the haemodynamic and biochemical variables in the non-ischaemic heart was investigated by comparing the values of these variables 10 min (time 35 min) and just before (time 45 min) induction of the second stenosis, in groups I–IV. Differences between the values of the various variables were evaluated for statistical significance by Wilcoxon's matched-pairs signed-ranks test (two-tailed probability). $P < 0.05$ was considered to be a significant difference.

RESULTS

Group I. Control experiments without constant heart rate

Mean coronary artery pressure decreased significantly from 69 mm Hg (0 min) to 24–27 mm Hg (median values 5, 10 and 15 min) during the first stenosis and from 72 mm Hg (45 min) to 24–25 mm Hg (50, 55 and 60 min) during the second stenosis (fig. 1). No significant differences could be detected between the mean coronary artery pressure values during the first and second stenosis. Systolic, diastolic and mean aortic pressure changed only slightly after induction of both the first and the second stenosis. Left ventricular dP/dt max decreased slightly during the first stenosis, but remained constant thereafter. Heart rate did not change significantly during the experiment (fig. 1).

No significant differences could be detected between the arterio–local venous differences of glucose, lactate and inorganic phosphate during the control periods, before the two periods of stenosis (fig. 2). Arterio–local venous differences of glucose increased during the first stenosis from 0.8 to 1.6–2.0 mmol

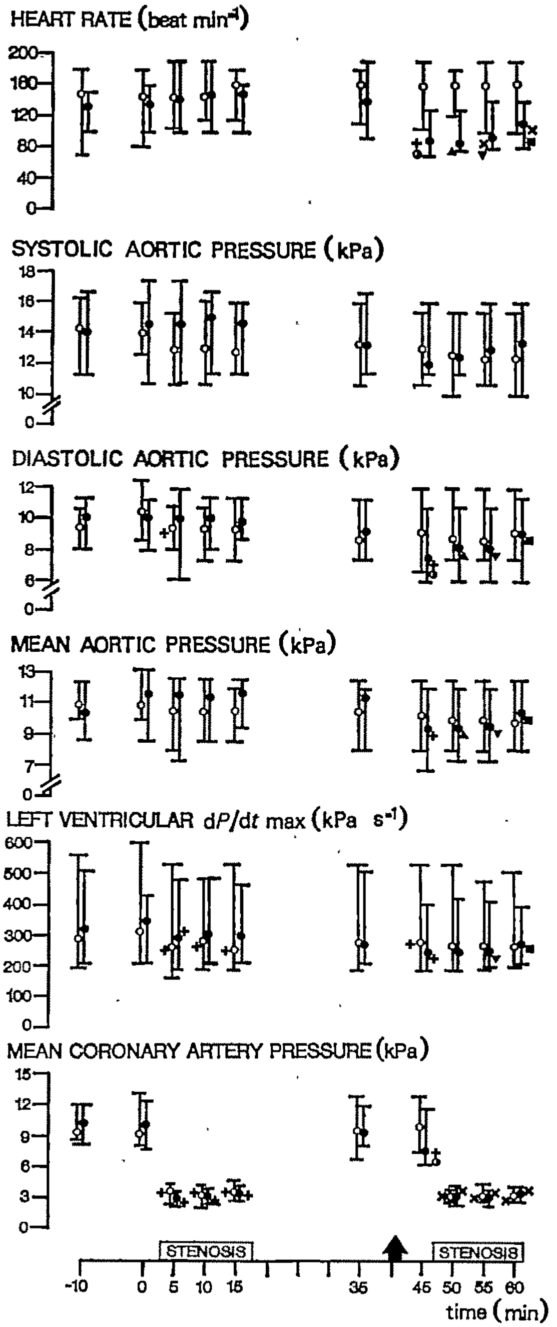

FIG. 1. Effect of fentanyl on heart rate, left ventricular dP/dt max, and aortic and coronary artery pressure, before and during coronary artery stenosis. Fentanyl 25 μg kg^{-1} i.v. was administered between 35 and 45 min (black arrow). Open circles represent control experiments ($n = 10$), closed circles fentanyl experiments ($n = 10$). The median values and the 95% limits of the various variables are shown. Significantly different from (time): + = 0 min; ◑ = 35 min; ▲ = 5 min; ▼ = 10 min; ■ = 15 min; × = 45 min.

($P < 0.05$) and during the second stenosis from 1.2 to 1.9–2.4 mmol ($P < 0.05$) (fig. 2). Lactate uptake changed to lactate release after induction of the stenosis. Arterio-local venous differences changed significantly from +0.20 to (−1.45)–(−1.25) mmol during the first and from +0.18 to (−1.65)–(−1.35) mmol during the second stenosis. Induction of coronary artery stenosis caused a net release of inorganic phosphate from the ischaemic area. Arterio-local venous differences varied during the first stenosis from −0.53 to −0.43 mmol and during the second between −0.25 and −0.32 mmol. The control values of the biochemical variables just before the first and the second stenosis were not significantly different (0 v. 45 min). Apart from significantly greater phosphate values 5 min after the onset of the first stenosis, as compared with the corresponding values during the second stenosis (50 min), no significant differences could be detected between the biochemical variables during the first and second stenosis (fig. 2).

Group II. Fentanyl without constant heart rate

Mean coronary artery pressure decreased significantly from 77 mm Hg (0 min) to 22–25.5 mm Hg during the first period of stenosis ($P < 0.05$). After administration of fentanyl 25 μg kg^{-1} i.v. 5 min before the onset of the second stenosis, mean coronary pressure decreased significantly from 69 to 58 mm Hg ($P < 0.05$). Subsequent induction of stenosis decreased this pressure to 24–25.5 mm Hg ($P < 0.05$). These values were not significantly different from the corresponding values during the first period of stenosis (fig. 1).

Fentanyl caused a decrease in heart rate ($P < 0.05$). During the second stenosis heart rate increased gradually ($P < 0.05$) 10 and 15 min after induction of the stenosis, but remained less than during the first stenosis ($P < 0.05$). Left ventricular dP/dt max, diastolic and mean aortic pressure decreased slightly, but significantly, after the administration of fentanyl. During the second period of stenosis the values of these haemodynamic variables were significantly smaller than their corresponding values during the first stenosis. There were no significant changes in aortic systolic pressure.

Fentanyl 25 μg kg^{-1} i.v. did not influence the arterio-local venous differences of glucose and

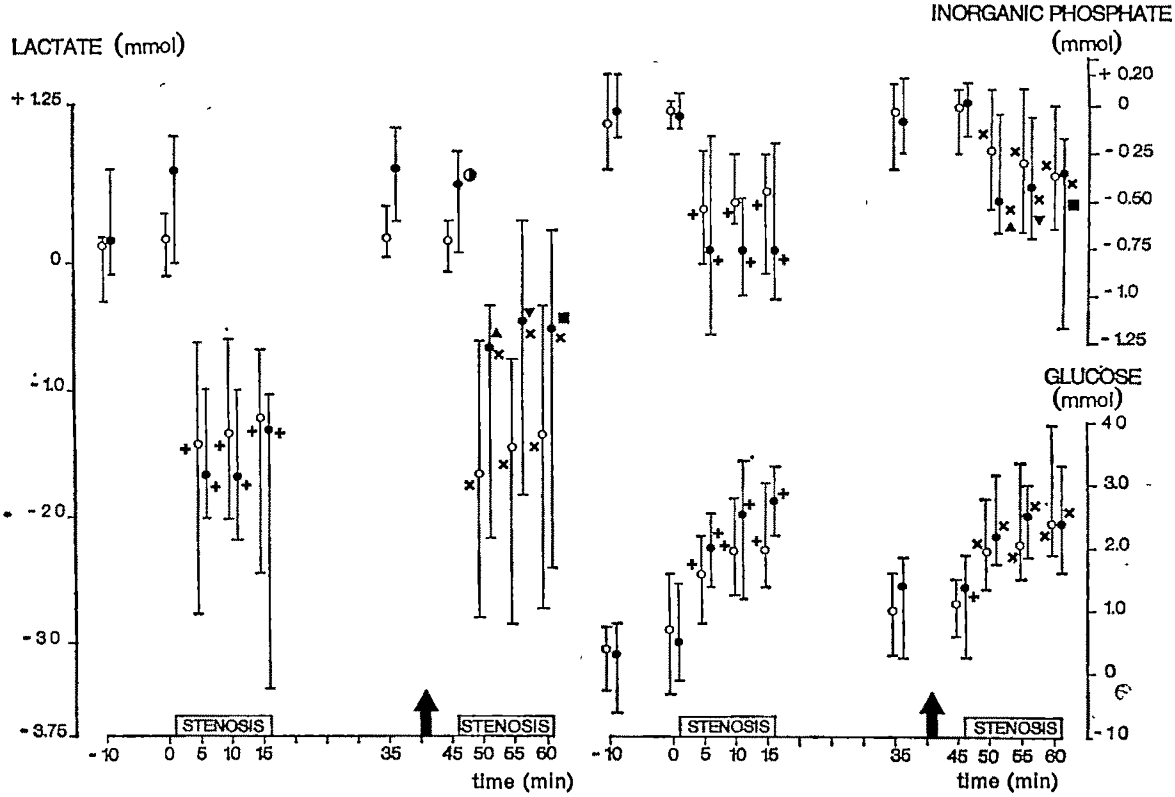

FIG. 2. Effect of fentanyl on arterio–local venous differences of lactate, glucose and inorganic phosphate before and during coronary artery stenosis. Heart rate was not kept constant. Fentanyl 25 $\mu g\ kg^{-1}$ i.v. was administered between 35 and 45 min (black arrow). Open circles represent control experiments ($n = 10$) and closed circles fentanyl experiments ($n = 10$). The median values and the 95% limits of the various variables are shown. Significantly different from (time): + = 0 min; ◑ = 35 min; ▲ = 5 min; ▼ = 10 min; ■ = 15 min; × = 45 min.

inorganic phosphate during the prestenosis control period, but it caused a slight decrease in arterio–local venous difference of lactate ($P < 0.05$) (fig. 2). No significant differences could be detected between the arterio–local venous differences of lactate and inorganic phosphate during the control periods, before the two periods of stenosis (0 and 45 min, respectively). Arterio–local venous differences of glucose showed a small, but significant increase during the control period before the second stenotic period. After induction of the second stenosis arterio–local venous differences of inorganic phosphate and lactate were significantly ($P < 0.05$) less negative than the corresponding values during the first period of stenosis (fig. 2). No consistent difference was found between the values of arterio–local venous difference of glucose during both periods of stenosis.

Group III. Control experiments with constant heart rate (140 beat min^{-1})

Mean coronary artery pressure decreased significantly during the first and second periods of stenosis and varied in these periods between 21–22 mm Hg and 21–22.5 mm Hg respectively (fig. 3). No significant differences could be detected between the mean coronary artery pressure values during the first and second stenosis. Apart from a small but significant decrease in left ventricular dP/dt max 5 min after induction of the first stenosis no significant changes in this variable were found. Systolic aortic pressure decreased from 100 to 89 mm Hg during the first period of stenosis, but remained constant thereafter. Induction of stenosis had no significant effect on mean and diastolic aortic pressure, with one exception. Diastolic aortic pressure was reduced slightly 10 min

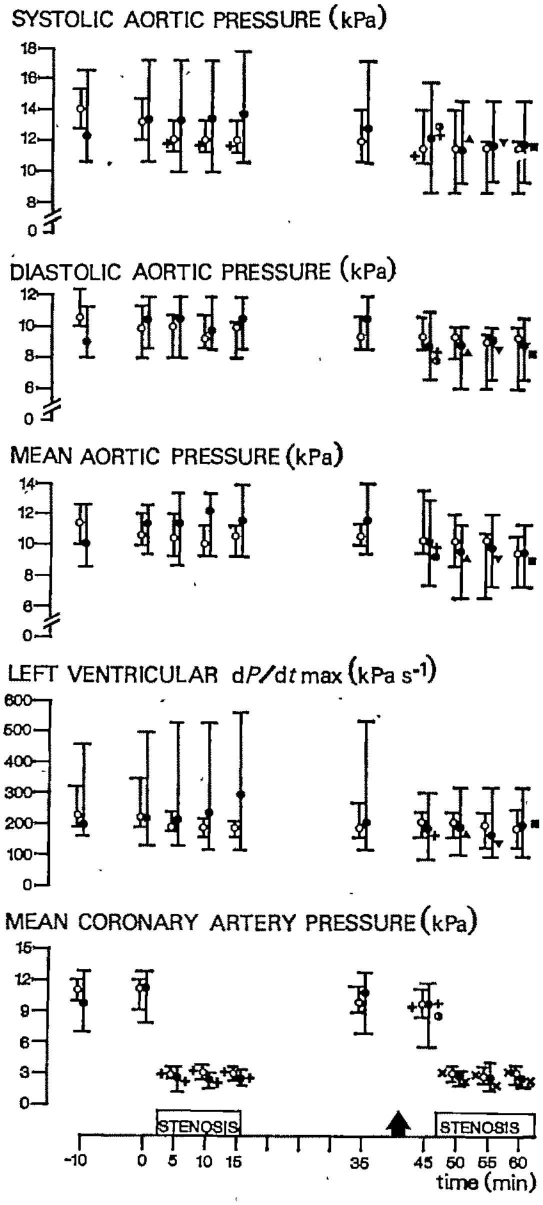

FIG. 3. Effect of fentanyl on left ventricular dP/dt max, and aortic and coronary artery pressure, before and during coronary artery stenosis. Heart rate was kept constant at 140 beat min^{-1}. Fentanyl 25 µg kg^{-1} i.v. was administered between 35 and 45 min (black arrow). Open circles represent control experiments ($n = 10$), closed circles fentanyl experiments ($n = 6$). The median values and the 95% limits of the various variables are shown. Significantly different from (time): + = 0 min; ◑ = 35 min; ▲ = 5 min; ▼ = 10 min; ■ = 15 min; × = 45 min.

after induction of the second stenosis. The control values of the biochemical variables just before the first and second stenosis were not significantly different (0 *v.* 45 min) (fig. 4). The changes in arterio-local venous differences of lactate and inorganic phosphate were similar after induction of the first and the second stenosis. Arterio-local venous differences of glucose increased from 0.5 to 1.1–2.1 mmol during the first stenosis and from 0.4 to 1.5–2.7 mmol during the second stenosis (fig. 4). The value, measured 10 min after the onset of the second stenosis, was significantly greater than the corresponding values in the first period.

Group IV. Fentanyl with constant heart rate (140 *beat min*$^{-1}$)

In the experiments in which heart rate was kept constant, fentanyl caused a significant decrease ($P < 0.05$) in systolic, diastolic and mean aortic pressure and mean coronary artery pressure (fig. 3). Coronary artery pressure decreased from 80 to 72 mm Hg. Mean coronary artery pressures, measured during the first and second stenosis, were not significantly different and varied between 17–19.5 mm Hg and 16.5–19.5 mm Hg respectively. During the second stenosis systolic, diastolic and mean aortic pressure were significantly smaller ($P < 0.05$) than during the first stenosis (fig. 3). Although no significant difference was found between the values of left ventricular dP/dt max 10 min and just before induction of the second stenosis, the latter value was smaller ($P < 0.05$) than its corresponding value before the first stenosis. Yet left ventricular dP/dt max was significantly smaller during the second than during the first stenosis ($P < 0.05$). Administration of fentanyl had no effect on arterio-local venous differences of glucose, lactate and inorganic phosphate during the control period before the second stenosis. The control values of the biochemical variables just before the first and the second stenosis were not significantly different (fig. 4). Arterio-local venous differences of glucose and inorganic phosphate during the second stenosis did not differ significantly from those during the first stenosis. Arterio-local venous differences of lactate were less negative during the second period of stenosis compared with the values during the first period. Only 10 min after induction of the stenosis, the arterio-local venous differences of lactate were significantly less negative during the second than during the first stenosis ($P < 0.05$) (fig. 4).

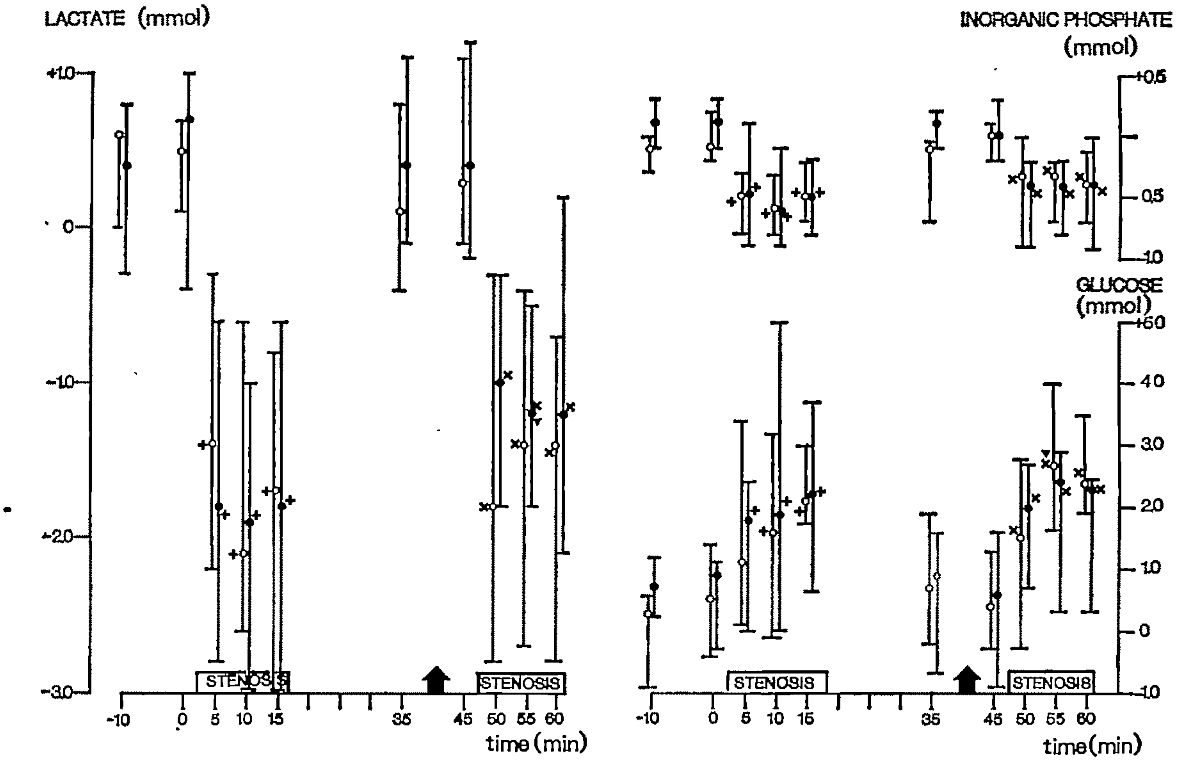

FIG. 4. Effect of fentanyl on arterio–local venous differences of lactate, glucose and inorganic phosphate, before and during coronary artery stenosis. In this series of experiments heart rate was kept constant at 140 beat min^{-1}. Fentanyl 25 μg kg^{-1} i.v. was administered between 35 and 45 min (black arrow). Open circles represent control experiments ($n = 10$), closed circles fentanyl experiments ($n = 6$). The median values and the 95% limits of the various variables are shown. Significantly different from (time): + = 0 min; ▼ = 10 min; × = 45 min.

DISCUSSION

The present study indicates that fentanyl 25 μg kg^{-1} reduced heart rate, left ventricular dP/dt max and aortic pressure. Since the release of inorganic phosphate and lactate from ischaemic heart tissue was reduced, fentanyl may prevent excessive breakdown of energy-rich phosphates and high rate of anaerobic production of lactate by decreasing the energy demand of the partially ischaemic myocardium. Results from experiments in which the heart rate was kept constant suggest that the negative chronotropic effect of fentanyl may be the most important factor in the beneficial effect of this drug on the ischaemic myocardium.

The reproducibility of the degree of ischaemia was indicated by the non-significant differences between the arterio–local venous differences of glucose, lactate and inorganic phosphate during the first and second stenosis at a comparable degree of coronary artery narrowing (there was no significant difference in mean coronary artery pressure during the first and second stenosis). This reproducible degree of ischaemia was achieved with and without a constant heart rate. Arterial and local venous concentrations of glucose and lactate were determined, to obtain information on aerobic and anaerobic carbohydrate metabolism in the left ventricular wall. Inorganic phosphate was measured since the increase of the concentration of this compound in local venous blood gives an indication of the degree of breakdown of energy-rich phosphates in the ischaemic heart tissue (Owen et al., 1970).

Stenosis was maintained for not longer than 15 min. Longer periods of ischaemia result in irreversible damage to the affected myocardium (unpublished observations) and the advantage of using the animal as its own control is lost. A period of stabilization between the periods of stenosis of longer than 30 min might improve the model. In the control experiments the arterio–local venous differences of inorganic phosphate were smaller during the second stenosis and this indicates that a period of 30 min is too brief for full restoration of the energy-rich phosphates.

An additional advantage of the present model is that, by partial occlusion of a major coronary artery, blood is obtained from a large, still perfused ischaemic area so that collateral circulation is not necessary for collecting local venous blood as in models in which ischaemia is induced by total occlusion of a small side branch of the interventricular artery (Owen et al., 1970; Opie et al., 1972). Moreover, partial occlusion (stenosis) of a coronary artery does not affect blood flow to the collateral areas (Jageneau et al., 1975).

Mean coronary artery pressure, as measured distal to the stenosis in a small side branch of the interventricular artery, rather than the reduction of mean blood flow in this artery, was used to estimate the degree of coronary artery narrowing. Under these conditions, the determination of pressure is easier and more accurate (Van der Meer and Reneman, 1972). Moreover, coronary artery pressure provides an indication of the contribution of collateral blood flow to the ischaemic area.

In the fentanyl experiments without constant heart rate (group II) the significantly reduced release of lactate and inorganic phosphate during the second stenosis indicates that, in the presence of fentanyl 25 μg kg^{-1} i.v., a comparable degree of coronary artery stenosis resulted in a decrease in anaerobic energy production and in a less pronounced breakdown of energy-rich phosphates. These changes were not seen in the control experiments (group I). It is likely that the diminished energy demand resulted from the decrease in heart rate, left ventricular dP/dt max and mean aortic pressure seen after the administration of fentanyl. The latter finding is in agreement with the results obtained by Gardocki and Yelnosky (1964), Freye (1974), Eisele and others (1975), Liu and others (1976), Patschke, Gethmann and others (1976) and Patschke, Hesse and others (1976) who showed that fentanyl decreased the energy demand of the left ventricle in hearts with an unimpeded coronary circulation. The gradual increase in heart rate during the second stenosis probably resulted from the decreasing activity of fentanyl during the experimental period. This increase in heart rate, however, was not reflected in the biochemical measurements.

To differentiate chronotropic and other effects of fentanyl on myocardial metabolism during ischaemia, heart rate was kept constant at 140 beat min^{-1} in an additional series of experiments (group IV). After the administration of fentanyl, left ventricular dP/dt max and systolic, diastolic and mean aortic pressure were significantly decreased (the same order of magnitude as in the experiments without constant heart rate) during the second stenosis as compared with the first, but no difference in arterio–local venous differences of inorganic phosphate could be detected. The arterio–local venous differences of lactate were less negative during the second stenosis, but these changes were less pronounced than in the experiments without constant heart rate. Only the values measured 10 min after the onset of stenosis differed significantly from the corresponding values during the first stenosis. This change in arterio–local venous differences of lactate was not seen in the control experiments with a constant heart rate (group III).

From the experiments performed with and without constant heart rate it may be concluded that the negative chronotropic effect of fentanyl is the major cause of the decrease in energy demand of the ischaemic myocardium. At slower heart rates the ischaemic myocardium benefits not only from the decreased energy demand, but also from the prolonged diastolic perfusion time.

Although it is difficult to extrapolate to clinical practice, it is likely that the use of fentanyl may be beneficial during anaesthesia, especially when the myocardium has a compromised circulation as a result of coronary artery stenosis.

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EFFET PRONONCE DU FENTANYL SUR L'HEMODYNAMIQUE, L'UTILISATION MYOCARDIALE DES GLUCIDES ET LE DEGAGEMENT DE PHOSPHATE PENDANT UNE ISCHEMIE

RESUME

On a fait des recherches sur l'effet qu'a le fentanyl, administré par voie intraveineuse à des chiens à raison de 25 µg/kg de poids du corps, sur l'hémodynamique du ventricule gauche, l'utilisation myocardiale des glucides et le dégagement de phosphate. On a pu obtenir un certain degré de reproductibilité de l'ischémie par l'occlusion partielle (sténose) de l'artère interventriculaire, à l'aide d'un manchon gonflable. En provoquant la sténose à deux reprises, on a pu utiliser l'animal comme étant son propre témoin. Les différences artérielles/veineuses locales de la glucose ont augmenté pendant l'ischémie et le myocarde ischémique a dégagé du lactate et du phosphate inorganique. Le fentanyl administré avant la seconde sténose a diminué la fréquence cardiaque et, à un degré moindre, la pression aortique moyenne de même que la d*P*/d*t* (max) ventriculaire gauche. Le dégagement de lactate et de phosphate inorganique a diminué pendant la période d'ischémie. Ces constatations laissent penser que le fentanyl empêche une décomposition excessive des phosphates riches en énergie ainsi qu'un taux de production anaérobie élevé de lactate, en diminuant la demande en énergie du myocarde ischémique.

DIE AKUTE WIRKUNG VON FENTANYL AUF HAEMODYNAMISCHE UND MYOKARDIALE KOHLEHYDRATVERWERTUNG UND PHOSPHATABGABE BEI ISCHÄMIE

ZUSAMMENFASSUNG

Die Wirkung von Fentanyl (25 µg/kg Körpergewicht, intravenös) auf die linksventrikuläre, hämodynamische und myokardiale Kohlehydratverwertung und Phosphatabgabe bei Ischämie wurde untersucht. Ein reproduzierbares Ausmass von Ischämie konnte durch partielle Verstopfung (Stenose) der intraventrikulararterie mittels einer aufblasbaren Manschette erzielt werden. Die zweimalige Hervorrufung der Stenose ermöglichte es, das Versuchstier zur eigenen Kontrolle zu verwenden. Die Unterschiede zwischen arteriellem und venösem Glukosegehalt verstärkten sich während der Ischämie, und aus dem ischämischen Myokardium wurden Laktat und inorganische Phosphate abgegeben. Fentanyl, vor der zweiten Stenose verabreicht, verringerten die Herztätigkeit und—in geringerem Ausmass—den mittleren Aortadruck und das linksventrikuläre $dP/dt_{\max}$. Die Abgabe von Laktat und inorganischem Phosphat war während der Ischämie-Periode verringert. Diese Ergebnisse lassen erkennen, dass Fentanyl den übermässigen Abbau der energiereichen Phosphate und eine starke anärobische Produktion von Laktat dadurch verhindert, dass der Energiebedarf des ischämischen Myokardiums verringert wird.

EFECTO AGUDO DEL FENTANILO EN HEMODINAMICA Y UTILIZACION DE CARBOHIDRATO MIOCARDIAL, Y LIBERACION DE FOSFATO DURANTE ISQUEMIA

SUMARIO

Se averiguó el efecto de 25 μg/kg de peso corporal de fentanilo i.v. en la hemodinámica ventricular izquierda, la utilización del carbohidrato miocardial y la liberación de fosfato durante isquemia en perros. Al usar esposas inflables, se pudo lograr un grado reproducible de isquemia mediante la oclusión parcial (estenosis) de la arteria interventricular. Induciendo la estenosis dos veces, fue posible usar al animal como su propio control. Las diferencias de glucosa arterio–venosa local aumentaron durante la isquemia y el miocardio isquémico liberó fosfato inorgánico y lactato. La administración de fentanilo antes de la segunda estenosis redujo el ritmo cardíaco y, en menor grado, la presión aórtica media y el máximo d*P*/d*t* ventricular izquierdo. La liberación de lactato y de fosfato inorgánico disminuyó durante el periodo de isquemia. Estos resultados sugieren que el fentanilo impide la ruptura excesiva de los fosfatos ricos en energía y un ritmo elevado de producción anaeróbica de lactato, al reducir la demanda energética del miocardio isquémico.

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EFFECT OF NITROUS OXIDE ON THE CARDIOVASCULAR SYSTEM AND CORONARY CIRCULATION OF THE DOG

J. THORBURN, G. SMITH, J. P. VANCE AND D. M. BROWN

SUMMARY

A comparison was made in seven dogs anaesthetized with pentobarbitone of cardiovascular measurements during ventilation with 65–70% nitrous oxide in oxygen and ventilation with 65–70% nitrogen in oxygen. The substitution of nitrous oxide for nitrogen was found to be associated, after 15 min, with a significant decrease in cardiac output and significant increases in right atrial and left ventricular end-diastolic pressure and systemic vascular resistance. There was no significant change in mean coronary artery flow, coronary vascular resistance or myocardial oxygen consumption.

Previous laboratory studies of the systemic cardiovascular effects of nitrous oxide have yielded conflicting results. Lundborg, Milde and Theye (1966) and Smith and Corbascio (1966) found little cardiovascular effect, whereas Craythorne and Darby (1965) found evidence of myocardial depression. Results of clinical studies of the effect of nitrous oxide have been at variance also. For examples, Bahlman and colleagues (1971) found no evidence of cardiovascular depression, whereas Eisele and Smith (1972) observed marked depression of cardiac function. Certainly different models, techniques and methods have been utilized and these may account for the divergent results.

There are relatively few studies of the effects of nitrous oxide on the coronary circulation. The present investigation was designed to study the effect of nitrous oxide on canine coronary blood flow together with any associated changes in the systemic circulation.

METHODS

Anaesthesia was induced in seven greyhounds (weight range 21–29 kg) with thiopentone 15–20 mg kg^{-1} and pentobarbitone 30 mg kg^{-1}. Suxamethonium 50–100 mg was given i.v. to facilitate endotracheal intubation. Intermittent positive pressure ventilation with a mixture of oxygen in nitrogen was provided by a Palmer sine-wave pump, the ventilation being adjusted to produce Pa_{CO_2} 5.2 kPa. The inspired oxygen mixture was adjusted to produce Pa_{O_2} 12.0 kPa.

Catheters were inserted into the ascending aorta and left atrium via the left femoral vessels to permit pressure recording and blood sampling. Under radiographic control, a catheter was introduced into the coronary sinus via the internal jugular vein and a second catheter was inserted, via the carotid artery, into the left ventricle for the measurement of left ventricular end diastolic pressure (LVEDP) using an Elema–Schonander capacitance transducer. The frequency response of this catheter manometer system was found to be flat only to 25 Hz. Frequencies greater than this were filtered out electronically. Therefore, it is appreciated that, while this system produces acceptably accurate measurement of LVEDP, no great reliance can be placed on the accuracy of the measurement of dp/dt max. In view of the small changes which were noted in this variable, the results are not significant and are not reported. A Swan–Ganz catheter was introduced into the pulmonary artery under radiographic control for sampling of mixed venous blood. A left thoracotomy was performed, and after incision of the pericardium, a small length of the circumflex or anterior descending branch of the left coronary artery was dissected out carefully, and a suitable electromagnetic flow transducer with non-occlusive zero was applied and connected to a flow meter (Statham SP 2202). Similarly, a suitable flow probe was placed around the pulmonary artery. After satisfactory siting, the lung was reinflated and collapse minimized by the use of 5 cm H_2O positive end-expiratory pressure. Cardiac output was measured from the pulmonary artery flow probe. The accuracy of the Statham flow meter has been assessed against an absolute technique

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of measurement of flow and a correlation coefficient of 0.99 was found ($y = 1.134x - 9.00$) (Vance et al., 1979).

Blood-gas tensions and pH were measured using suitably calibrated electrodes (IL 213). Systemic arterial, pulmonary arterial and coronary sinus blood-gas tensions were corrected for the differences in temperature between the electrodes and the mid-oesophageal temperature of the animal. Blood oxygen content was calculated from the equation:

$$O_2 \text{ content (ml dl}^{-1}) = \text{Hb concn (g dl}^{-1}) \times 1.36 \times \% \text{ satn} + Pa_{O_2} \text{ (kPa)} \times 0.0232$$

This has been found to correlate satisfactorily with the Van Slyke method of measurement of blood oxygen content as used in this laboratory (Ledingham et al., 1970).

The techniques used in the preparation, and the calculation of derived variables, have been discussed in greater detail in a recent publication (Vance et al., 1979).

After surgery, a control period of 30 min was observed to allow the preparation to stabilize and duplicate measurements were obtained during ventilation with 65–70% nitrogen in oxygen to ensure that a steady baseline had been obtained. After this, measurements were obtained following 15 min ventilation of the lungs with either 65–70% nitrogen in oxygen or 65–70% nitrous oxide in oxygen. Subsequently, the inspired gas was changed and after 15 min the measurements were repeated. In each dog, four sets of measurement were obtained for ventilation alternately with either nitrous oxide in oxygen or nitrogen in oxygen and the order of presentation of the gases was randomized over the seven experiments. Mean values of measurement were obtained for the two sets of corresponding data for each animal and the mean values for the seven animals compared by two-tailed Student's *t* test for paired data.

RESULTS

No statistically significant changes occurred in arterial, pulmonary arterial or coronary sinus blood-gas measurements during the various phases of the study.

Nitrous oxide produced a 21% increase in peripheral resistance but no change in heart rate or arterial pressure (table I). In addition, myocardial contractility was depressed as revealed by an 11% decrease in cardiac output, a 27% increase in LVDEP and a 12% increase in right atrial pressure (table II).

Nitrous oxide produced no significant changes in mean or systolic coronary blood flow or coronary artery resistance. There was a small but statistically significant increase in diastolic coronary artery flow (table III). This was associated with a significant increase in myocardial oxygen availability (table IV), although total body oxygen availability decreased as did total body oxygen consumption. There was no change in myocardial oxygen consumption or extraction (table III).

TABLE I. *Effect of nitrogen in oxygen and nitrous oxide in oxygen mixtures on heart rate, mean arterial pressure and total peripheral resistance (mean ± SEM; n = 7)*

	N_2/O_2	N_2O/O_2	% Change from nitrogen phase	Significance
Heart rate (beat min^{-1})	156.0 ± 5.2	159.0 ± 4.8	—	n.s.
Mean arterial pressure (mm Hg)	138.0 ± 6.7	139.0 ± 6.3	—	n.s.
Total peripheral resistance (unit)	47.4 ± 6.23	57.3 ± 8.7	+21%	< 0.05

TABLE II. *Effect of nitrogen in oxygen and nitrous oxide in oxygen mixtures on cardiac function (mean ± SEM; n = 7)*

	N_2/O_2	N_2O/O_2	% Change from nitrogen phase	Significance
Cardiac output (litre min^{-1})	3.6 ± 0.43	3.2 ± 0.4	−11%	< 0.01
Mean right atrial pressure (mm Hg)	2.4 ± 0.3	2.8 ± 0.3	+12%	< 0.01
LVDEP (mm Hg)	11.2 ± 1.9	14.2 ± 2.2	27%	< 0.025

TABLE III. *Effect of nitrogen in oxygen and nitrous oxide in oxygen mixtures on the coronary circulation (mean ± SEM; n = 7)*

	N_2/O_2	N_2O/O_2	% Change from nitrogen phase	Significance
Mean coronary artery flow (ml min^{-1})	62 ± 7.8	64 ± 8.1	—	n.s.
Mean coronary artery resistance (unit)	255 ± 25.0	259 ± 24.0	—	n.s.
Systolic coronary artery flow (ml min^{-1})	36 ± 6.5	36 ± 6.0	—	n.s.
Diastolic coronary artery flow (ml min^{-1})	88 ± 10.0	95 ± 10.0	+8	<0.05

TABLE IV. *Effect of nitrogen in oxygen and nitrous oxide in oxygen on myocardial and total body oxygenation (mean ± SEM; n = 7)*

	N_2/O_2	N_2O/O_2	% Change from nitrogen phase	Significance
Myocardial				
Oxygen availability (ml min^{-1})	14.1 ± 1.8	14.8 ± 1.8	+7	<0.05
Oxygen extraction (%)	63.0 ± 2.2	61.0 ± 2.0	—	n.s.
Oxygen consumption (ml min^{-1})	9.0 ± 1.0	9.0 ± 1.0	—	n.s.
Total body				
Oxygen availability (ml min^{-1})	805.0 ± 98.0	724.0 ± 93.1	−10	<0.05
Oxygen extraction (%)	25.0 ± 1.9	26.0 ± 2.7	—	n.s.
Oxygen consumption (ml min^{-1})	177.0 ± 14.1	151.0 ± 10.7	−15	<0.05

DISCUSSION

The results of the present study reveal that nitrous oxide produced small but significant changes in cardiac output, mean right atrial pressure and left ventricular end-diastolic pressure which were consistent with a decrease in myocardial contractility. There were no significant changes in mean arterial pressure or heart rate, but nitrous oxide produced a significant increase in total systemic peripheral resistance.

Several earlier reports describing cardiovascular collapse in patients anaesthetized with oxygen and halothane in a closed circuit system following the introduction of nitrous oxide into the system suggested that nitrous oxide produced cardiovascular depression (Ap Ivor, 1959; Young and Lodge, 1959; Johnstone, 1961). However, the data in these earlier reports are difficult to interpret as a result of uncontrolled variables. Subsequently, there have been many controlled laboratory and clinical studies, some of which have indicated a dominant effect on myocardial contractility and some a dominant effect on the peripheral circulation (table V). These differences may be accounted for by the use of different species, different techniques of assessment of cardiovascular changes and myocardial contractility and the presence of different anaesthetic agents used for background anaesthesia. It is well known that myocardial contractility may be altered by inhalation anaesthetic agents, changes in arterial carbon dioxide tension and increased arterial oxygen tensions—factors which have varied in previous studies and which may have masked any changes produced by nitrous oxide. In table VI are listed the studies from table V in which myocardial contractility has been evaluated. In almost every instance there was a trend towards a reduction in myocardial contractility, although the authors' analyses revealed that the trend was not statistically significant.

TABLE V. *Effect of nitrous oxide on mycardial contractility and peripheral resistance*

Investigators	Effect on myocardial contractility	Effect on peripheral resistance
Craythorne and Darby (1965)	Decrease	Not increased
Smith and Corbascio (1966)	Nil	Increase
Lundborg, Milde and Theye (1966)	Decrease	Increase
Hornbein and others (1969)	Nil	Nil
Smith and others (1970)	Nil	Increase
Bahlman and others (1971)	Increase	Increase
Eisele and Smith (1972)	Decrease	Increase
Stoelting, Revis and Longnecher (1972)	Nil	Nil
Stoelting and Gibbs (1973)	Decrease	Increase
Thornton and others (1973)	Nil	Not measured
Stoelting and others (1975)	Decrease	Nil
Eisele and others (1976)	Decrease	Increase

TABLE VI. *Studies taken from table V indicating the model used. The results column shows the effect of nitrous oxide on myocardial contractility. In some instances the authors observed mild depression, but analysis revealed it to be not statistically significant*

Investigator	Subject	Background anaesthesia	Subject ventilation	Inspired gas mixture control : experimental	Effect of N_2O on myocardial contractility
Craythorne and Darby (1965)	Dogs	Halothane	Controlled	Air : N_2O/O_2	↓Significantly
Smith and Corbascio (1966)	Dogs	Halothane	Controlled	$O_2 : N_2O/O_2$	↓Trend not significant
Lundborg, Milde and Theye (1966)	Dogs	Halothane	Controlled	$N_2/O_2 : N_2O/O_2$	Trend
Hornbein and others (1969)	Fit humans	Halothane, varying Pa_{CO_2} values	Spontaneous	$O_2 : N_2O/O_2$	None
Smith and others (1970)	Fit humans	Halothane	Controlled	Air/$O_2 : N_2O/O_2$	↓Trend in some aspects
Bahlman and others (1971)	Fit humans	Halothane	Controlled	$O_2 : N_2O/O_2$	Increase
Eisele and Smith (1972)	Fit humans	None	Spontaneous	$N_2/O_2 : N_2O/O_2$	Significant decrease
Stoelting, Revis and Longnecher (1972)	Ill humans	Halothane + curare	Spontaneous controlled	$N_2/O_2 : N_2O/O_2$	↓Trend not significant
Stoelting and Gibbs (1973)	Ill humans	Morphine	Spontaneous: assisted controlled	Air/$O_2 : N_2O/O_2$	Depression
Thornton and others (1973)	Ill humans	None	Spontaneous	$O_2/N_2 : N_2O/O_2$50%	↓Trend not significant
Stoelting and others (1975)	Ill humans	Fentanyl/ dropiderol	Spontaneous controlled	Air/$O_2 : N_2O/O_2$	Depression
Eisele and others (1976)	Ill humans	None	Spontaneous	$N_2/O_2 : N_2O/O_2$	Depression

There is little doubt that the cardiovascular effects of nitrous oxide in the intact animal preparation or human are small (tables V and VI) and these may be obscured by other physiological changes or pharmacological effects. *In vitro*, there is good evidence that nitrous oxide produces a decrease in myocardial contractility (Price and Helrich, 1955; Price, 1976). Although Goldberg, Young and Phear (1972) observed a decrease in myocardial contractility with nitrous oxide in papillary cardiac muscle, similar changes were seen with the same concentration of nitrogen. However, the production of hypoxia was invoked as the mechanism accounting for this paradox (Price, 1976).

In the systemic circulation, nitrous oxide would appear to exert effects similar to those of an alpha-adrenergic agonist (Cullen, 1972; Leighton and Koth, 1973). Thus, a reduction in forearm blood flow was found in subjects anaesthetized with nitrous oxide and subsequently there was an increase in the urinary excretion of catecholamines (Smith et al., 1970). In addition, Eisele and colleagues (1976) observed an increase in plasma noradrenaline concentrations in association with the administration of nitrous oxide in patients. It is interesting that, although pentobarbitone is usually associated with a reduction in sympathetic responses, Eisele and colleagues (1969) observed that awake animals with chronically implanted aortic flow meters exhibited the same type of responses to nitrous oxide as did animals anaesthetized with pentobarbitone. In addition, Millar and co-workers (1970) found that pentobarbitone did not alter the sympathetic response of animals to nitrous oxide.

It would be anticipated that the small effects of nitrous oxide on both myocardial contractility and peripheral resistance would be associated with negligible changes in the coronary circulation and this is confirmed by the results of the present study. Although a small increase in diastolic coronary blood flow occurred, there was no significant change in mean coronary artery flow or mean coronary artery resistance. No change in myocardial blood flow was found by Dottori and colleagues (1976) during ventilation of dogs with either 50% nitrogen in oxygen or 50% nitrous oxide in oxygen. When the concentration of nitrous oxide was increased to 80%, a decrease in coronary vascular resistance occurred, permitting an increase in myocardial blood flow. It is well known that hyperoxia produces vasoconstriction in the coronary circulation so this change may be interpreted as a reduction in the vasoconstrictive effect of oxygen rather than a vasodilator effect of nitrous oxide. In the present study, the concentration of nitrous oxide was 65–70%, and this value was chosen in order to produce a normal arterial oxygen tension. Under these circumstances, there was no change in mean coronary artery flow.

The systemic effects of nitrous oxide seen in the present study were similar to those found by previous investigators (table V) and comprise an increase in peripheral resistance and a reduction in cardiac output with an associated reduction in total body oxygen availability.

The clinical implications of the present study are small. However, it would be expected that in patients with impaired myocardial contractility and a high degree of resting sympathetic activity, the exhibition of nitrous oxide may be associated with detectable cardiovascular depression. Nitrous oxide would not be expected to have any direct effects on the coronary circulation, but changes in myocardial blood flow may occur secondary to alterations in myocardial contractility and external cardiac work.

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EFFET DU PROTOXYDE D'AZOTE SUR LE SYSTEME CARDIOVASCULAIRE ET SUR LA CIRCULATION CORONAIRE DU CHIEN

RESUME

On a fait une comparaison des mesures cardiovasculaires prises sur sept chiens anesthésiés à l'aide de pentobarbitone, pendant une ventilation à 65–70% de protoxyde d'azote dans de l'oxygène et pendant une ventilation à 65–70% d'azote dans de l'oxygène. La substitution de protoxyde d'azote par de l'azote a été associée, après 15 min, à une diminution importante du débit cardiaque et à des augmentations significatives de la pression diastolique d'extrémité de l'oreillette droite et du ventricule gauche, de même que de la résistance vasculaire systémique. Il n'y a eu aucune variation significative dans le débit artériel coronaire moyen, ni dans la résistance vasculaire coronaire, ni dans la consommation d'oxygène du myocarde.

WIRKUNG VON STICKOXYD AUF DAS KARDIOVASKULÄRE SYSTEM UND DEN KORONARKREISLAUF BEIM HUND

ZUSAMMENFASSUNG

Bei sieben mit Pentobarbiton narkotisierten Hunden wurden die kardiovaskulären Messungen während der Belüftung mit 65–70% Stickoxyd in Sauerstoff, und mit 65–70% Stickstoff in Saurestoff verglichen. Der Austausch von Stickoxyd mit Stickstoff ergab nach 15 Minuten einen deutlichen Abstieg im Herzminutenvolumen, sowie einen deutlichen Anstieg des enddiastolischen Druckes in rechtem Atrium und linkem Ventrikel, und einen Anstieg des systemischen Gefässwiderstandes. Der mittlere koronararterielle Fluss änderte sich kaum, ebensowenig wie der Koronargefässwiderstand oder der myokardiale Sauerstoffverbrauch.

EFECTO DEL OXIDO NITROSO SOBRE EL SISTEMA CARDIOVASCULAR Y LA CIRCULACION CORONARIA DEL PERRO

SUMARIO

En siete perros anestesiados por pentobarbitona, se hizo una comparación de las mediciones cardiovasculares durante ventilación con 65–70% de óxido nitroso en oxígeno, y ventilación con 65–70% de nitrógeno en oxígeno. Se comprobó que la substitución del óxido nitroso al nitrógeno se acompañaba, después de 15 min, de una disminución significativa del volumen-minuto cardíaco y de unos aumentos importantes de la presión diastólica terminal ventricular izquierda y auricular derecha y de la resistencia vascular sistémica. No hubo cambio significativo del flujo arterial coronario medio, de la resistencia vascular coronaria o del consumo miocardial de oxígeno.

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PHARMACOKINETICS OF FAZADINIUM IN PATIENTS WITH RENAL FAILURE

P. DUVALDESTIN, J. C. BERTRAND, D. CONCINA, D. HENZEL, L. LARENG AND J. M. DESMONTS

SUMMARY

The serum concentrations of fazadinium and its metabolites were measured in 14 surgical patients with end-stage renal failure and in 11 patients free from kidney disease undergoing abdominal surgery. A two-compartment open model was used in the pharmacokinetic analysis of the data. The elimination half-life ($T_{\frac{1}{2}}\beta$) was prolonged by 60% in patients with renal failure (from 85 to 140 min) and corresponded to a 30% decrease of the plasma clearance. The plasma concentration of the metabolites never exceeded 7% of the unchanged fazadinium. These results suggest that the duration of action will be less prolonged for fazadinium than for other non-depolarizing neuromuscular blocking drugs in patients with renal failure. A supplementary biliary pathway appears to be a possible explanation for the rapid elimination of fazadinium, even in patients with renal failure.

The use of neuromuscular blocking agents in patients with renal failure is complicated by delay in the elimination of these drugs. Like other non-depolarizing myoneural blocking drugs, fazadinium is excreted mainly unchanged in the urine in man (Duvaldestin et al., 1978). However, it has been observed that its duration of action was not prolonged significantly in patients with end-stage renal failure (Camu and D'Hollander, 1978). The aim of the present study was to investigate the influence of impaired renal function on the pharmacokinetics of fazadinium in anaesthetized patients.

METHODS

Fourteen patients in renal failure and 11 normal patients were studied. The patients in renal failure had either absent renal function or gross renal insufficiency necessitating haemodialysis, which was carried out 24–36 h before operation. The characteristics of the patients and of the surgical procedures are listed in table I.

The same anaesthetic procedure was used for all patients. Atropine 0.5 mg and droperidol 5–15 mg were given i.m. as premedication. Anaesthesia was induced with thiopentone 6–9 mg kg^{-1} and maintained with a 33% oxygen in nitrous oxide mixture delivered by mechanical ventilation. Phenoperidine or fentanyl were given in repeated doses. Fazadinium was administered in a single dose of 1, 1.5 or 2 mg kg^{-1} to all the patients according to the expected duration of the surgical procedure. Atropine 0.5 mg and prostigmine 2 mg were administered in three control patients and in all patients with renal failure at the end of the surgical procedure.

Serial blood samples were obtained from the 5th to the 300th min after the injection of fazadinium. In six control patients, urine samples were collected each hour during the first 6 h and for up to 24 h from an indwelling catheter. The concentration of fazadinium was determined in the plasma and urine according to the fluorimetric method of Pastorino (1978), using a Jobin Yvon JY 3D spectrofluorimeter. This method allows the determination of fazadinium and its metabolites in plasma and urine. The pharmacokinetics of fazadinium were analysed according to a two-compartment open model which was detailed in a previous report (Duvaldestin et al., 1978). Two-tailed Student's *t* tests were used to evaluate the differences between the two groups of patients. *P* less than 0.05 was considered statistically significant.

RESULTS

The pharmacokinetic variables are presented in table II. The half-lives corresponding to the distribution or α phase ($T_{\frac{1}{2}}\alpha$) and to the elimination or β phase ($T_{\frac{1}{2}}\beta$), the plasma clearance (*Cl*), the total apparent volume of distribution (*V*d) and the volume of the central compartment (V_1) are listed in table III. A slight but significant ($P < 0.05$) increase in $T_{\frac{1}{2}}\alpha$ was

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TABLE I. *Details of patients studied*

Patient	Sex	Age (yr)	Weight (kg)	Height (cm)	Operation	Plasma creatinine (mg litre^{-1})
1	M	31	67	173	Kidney transplantation	109
2	M	31	61	167	Kidney transplantation	45
3	M	20	65	185	Kidney transplantation	112
4	F	35	45	131	Kidney transplantation	33
5	M	45	75	186	Kidney transplantation	66
6	F	27	50	155	Kidney transplantation	126
7	M	25	60	171	Kidney transplantation	138
8	M	33	68	170	Kidney transplantation	77
9	M	49	75	171	Kidney transplantation	103
10	M	31	67	173	Removal of transplanted kidney	102
11	F	27	50	155	Renal biopsy	59
12	M	57	49	167	Bilateral nephrectomy	75
13	F	42	60	172	Nephrectomy	118
14	F	28	50	157	Bilateral nephrectomy	70

TABLE II. *Pharmacokinetic variables. Significantly different from the normal group*: $^{**}P<0.01$; $^{***}P<0.001$

	Normal group (mean ± SEM) ($n = 11$)	Renal failure group (mean ± SEM) ($n = 14$)
V_1 (ml kg^{-1})	121 ± 14	200 ± 16**
V_2 (ml kg^{-1})	93 ± 9	82 ± 12
k_{12} (h^{-1})	1.32 ± 0.24	1.04 ± 0.32
k_{21} (h^{-1})	1.72 ± 0.21	1.92 ± 0.40
k_{EL} (h^{-1})	1.08 ± 0.09	0.56 ± 0.07***

TABLE III. *Plasma half-lives of the distribution phase* ($T_{\frac{1}{2}}\alpha$) *and elimination phase* ($T_{\frac{1}{2}}\beta$), *total apparent volume of distribution* (*Vd*) *and plasma clearance* (*Cl*) *of fazadinium in* 11 *normal patients and in* 14 *patients with renal failure. Values represent the mean ± SEM. Significantly different from the normal group*: $^{*}P<0.05$; $^{***}P<0.001$

	Normal patients ($n = 11$)	Patients with renal failure ($n = 14$)
$T_{\frac{1}{2}}\alpha$ (min)	13 ± 2	22 ± 4*
$T_{\frac{1}{2}}\beta$ (min)	85 ± 5	140 ± 17***
Cl (ml min^{-1} m^{-2})	91 ± 12	65 ± 10
Vd (ml kg^{-1})	287 ± 36	310 ± 77

observed in patients with renal failure. This increase in the duration of the distribution phase can be explained by an increase in the volume of the central compartment (V_1) from 121 ± 14 to 200 ± 16 ml kg^{-1} (table II). Prolongation of the elimination half-life from 85 ± 5 to 140 ± 17 min was observed in patients with renal failure. This prolongation of the elimination phase corresponded to a 33% decrease in the plasma clearance.

The concentration of metabolites in the plasma or in the central compartment always remained very low, never exceeding 7% of the concentration of unchanged fazadinium (fig. 1). During the first 15 min, the mean plasma concentration of the metabolites in patients with renal failure was about twice that of the controls. However, this difference is of little importance compared with the plasma concentration of unchanged drug. In the control group, the study of urinary elimination showed that most of the fazadinium was excreted within the first 6 h. During this period the average recovery was 46% of the dose and during the following 18 h no more than 3% of the dose was excreted (fig. 2). The highest individual urinary excretion never exceeded 60% of the injected dose. The proportion excreted in the form of metabolites was always very low, accounting for no more than 1% of the dose after 24 h.

DISCUSSION

The results of this investigation indicate that the main alteration of the pharmacokinetics of fazadinium is a modest prolongation, by 60%, of the half-life of the elimination phase. This change was primarily a result of a decrease in the plasma clearance. No significant increase in the total apparent volume of distribution of this hydrophilic drug was observed. In comparison with the other muscle relaxants, these changes in the pharmacokinetics of fazadinium induced by renal failure, are modest. In the absence of kidney function, the half-life of the elimination phase was prolonged by 500%, from 100 to 500 min, for pancuronium (McLeod, Watson and Rawlins, 1976), by 70%, from 152 to 256 min, for tubocurarine

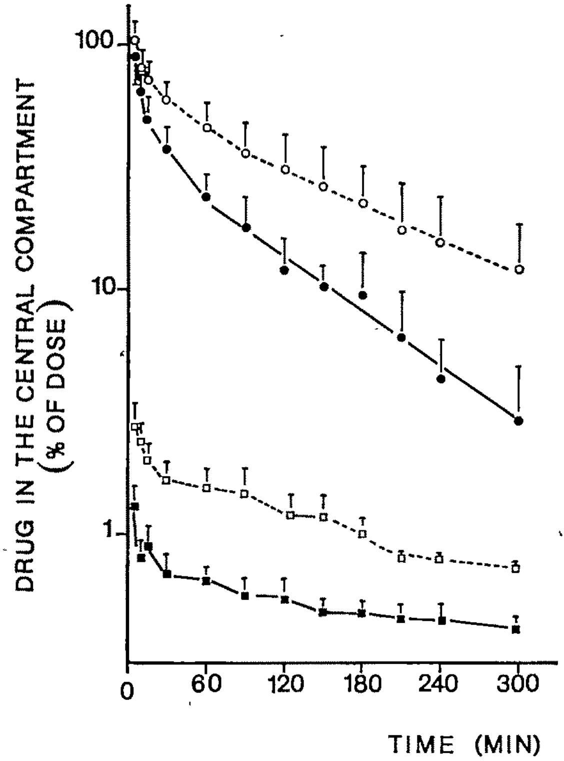

FIG. 1. Elimination of fazadinium from the central compartment in man after an i.v. injection. Semi-logarithmic plot of the amount of fazadinium and its metabolites present in the central compartment (±SEM) in normal patients and in patients with renal failure. Fazadinium: ●——● = normal, ○---○ = renal failure; fazadinium metabolites: ■——■ = normal, □---□ = renal failure.

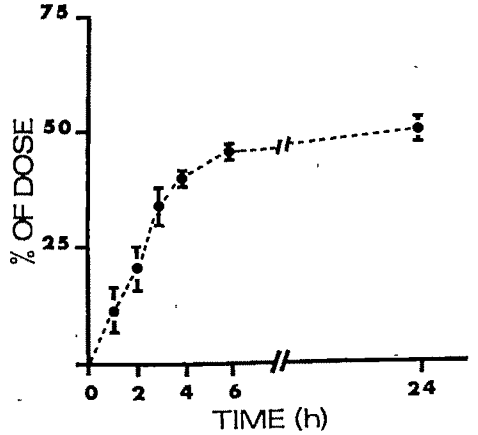

FIG. 2. Cumulative urinary excretion (mean±SEM) of fazadinium in six normal patients after i.v. injection of a single dose. Urine samples were obtained separately from an indwelling urethral catheter.

(Miller et al., 1977) and by about 400% for alcuronium (Raaflaub and Frey, 1972). Camu and D'Hollander (1978) showed no significant prolongation of the duration of the neuromuscular block in patients with renal failure after moderate doses of fazadinium (0.25–1 mg kg^{-1}). This finding can be explained by the relatively minor changes in the pharmacokinetics of this drug induced by renal failure and by the low doses which were administered. With low doses of neuromuscular blocking drugs the duration of action is influenced mainly by the α phase or the rate of disruption of drug–receptor union (Feldman and Tyrrell, 1970); for higher doses the β phase becomes the predominant factor, particularly when renal failure slows the rate of elimination (Shanks, Somogyi and Triggs, 1978). A prolongation of the elimination phase will be more likely to influence the rate of recovery from the neuromuscular blockade than the overall duration of the neuromuscular blockade (Somogyi, Shanks and Triggs, 1977). The interval between the recovery of the twitch height from 25% to 75% is a better index by which to study the influence of excretion processes on the duration of action. These twitch height values are observed at the time at which the elimination phase is the main process influencing the profile of decay of the plasma concentration for normal doses of non-depolarizing neuromuscular blocking drugs. Furthermore, during this recovery phase, a good correlation can be demonstrated between the plasma concentration of pancuronium and the depression of twitch height (Agoston et al., 1977; Shanks, Somogyi and Triggs, 1978).

If the interval between the recovery of the twitch height from 25% to 75% is used, a prolongation of the duration of fazadinium 1 mg kg^{-1} will be shown in patients with renal failure (Camu and D'Hollander, 1978). In our series, a large interindividual variation in the slope of the β phase was observed in the group with kidney failure; $T_{\frac{1}{2}}\beta$ varied from 60 to 310 min. One patient (No. 14) required mechanical ventilation for 10 h for prolonged neuromuscular blockade after 2 mg kg^{-1} of fazadinium which was not antagonized by neostigmine. The elimination half-life in this patient was 169 min. During the period of this study, none of the patients undergoing kidney transplantation exhibited a rapid improvement of their renal function which could have explained partly the individual variation in the pharmacokinetics of fazadinium. The creatinine clearance varied in the range 5–21 ml min^{-1} (mean: 13 ml min^{-1}) 24 h after transplantation. The relatively rapid decay of the plasma concentration in patients with renal failure remains unclear. Normally, fazadinium is excreted mainly unchanged in urine as are most other non-depolarizing relaxants. The mechanism of renal excretion is probably ultrafiltration. This excretion is rapid, occurring mainly during the first 6 h which correspond to the period of clinical anaesthesia. The plasma clearance of fazadinium is often great, greater than the creatinine clearance, suggesting an extra-renal pathway of excretion. Hepatic biotransformation of fazadinium by microsomal azoreductase represents a minor pathway of elimination. This study suggests that biliary excretion may represent an alternative pathway of excretion for fazadinium which could be quantitatively more important than for other muscle relaxants. Approximately the same amounts of myoneural blocking agents are normally excreted in the bile within 24 h in man; it accounts for about 10% of the injected dose for pancuronium (Agoston et al., 1973), alcuronium (Raaflaub and Frey, 1972) and tubocurarine (D. K. Meijer, personal communication). An increase in the biliary elimination as compared with other muscle relaxants has been afforded as a possible explanation of the short half-life of the elimination phase in normal patients (Duvaldestin et al., 1978). This supplementary pathway will be of greatest importance during renal insufficiency and offers a reasonable explanation for the relatively fast elimination of fazadinium in patients with renal failure.

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PHARMACOCINETIQUE DU FAZADINIUM CHEZ LES MALADES SOUFFRANT D'UNE INSUFFISANCE RENALE

RESUME

Les concentrations de fazadinium et de ses métabolites dans le sérum ont été mesurées sur 14 patients souffrant d'une insuffisance rénale au stade final, de même que sur 11 patients n'ayant aucune maladie des reins, mais tous subissant une intervention chirurgicale à l'abdomen. On a utilisé un modèle ouvert à deux compartiments pour l'analyse pharmacocinétique des données. La demi-vie de l'élimination ($T_{\frac{1}{2}}\beta$) a été prolongée de 60% sur les malades souffrant d'insuffisance rénale (de 85 à 140 min) ce qui a correspondu à une diminution de 30% du coefficient d'épuration plasmatique. Les concentrations de métabolites dans le plasma n'ont jamais été supérieures à 7% du fazadinium non modifié. Ces résultats laissent penser que la durée de l'action sera moins prolongée pour le fazadinium que pour les autres agents de blocage neuromusculaire non dépolarisants chez les malades souffrant d'insuffisance rénale. Une voie d'accès biliaire supplémentaire semble être une explication possible de l'élimination rapide du fazadinium, même chez les malades souffrant d'insuffisance rénale.

PHARMAKOKINETISCHE EIGENSCHAFTEN VON FAZADINIUM BEI PATIENTEN MIT NIERENVERSAGEN

ZUSAMMENFASSUNG

Die Serumkonzentrationen von Fazadinium wurde bei 14 operativen Patienten mit Nierenversagen im letzten Stadium und bei 11 Patienten ohne Nierenerkrankung aber bei Unterleibsoperationen gemessen. In der pharmakokinetischen Analyse der Daten wurde ein zweiteiliges, offenes Modell verwendet. Die Ausscheidungs-Halbwertszeit ($T_{\frac{1}{2}}\beta$) wurde bei Patienten mit Nierenversagen um 60% (von 85 auf 140 Minuten) verlängert, was einem 30%igen Abstieg in der Plasmaklärung entsprach. Die Plasmakonzentrationen der Metaboliten uberstieg niemals 7% des unveränderten Fazadiniums. Diese Resultate zeigen, dass die Wirkungsdauer für Fazadinium weniger verlangert ist als die anderer nicht-depolarisierender Drogen bei Patienten, bei denen Nierenversagen besteht. Ein zusätzlicher Gallenweg scheint eine mogliche Erklärung für die rapide Ausscheidung von Fazadinium zu sein–selbst bei Patienten mit Nierenversagen.

FARMACOCINETICA DEL FAZADINIO EN PACIENTES CON DEFICIENCIA RENAL

SUMARIO

Se midieron concentraciones serosas de fazadinio y de sus metabolitos en 14 pacientes de cirujía con deficiencia renal terminal y en 11 pacientes sin enfermedad renal, sometidos a cirujía abdominal. Se usó un modelo abierto de dos compartimentos para el análisis farmacocinético de los datos. Se extendió en un 60% la vida media de eliminación ($T_{\frac{1}{2}}\beta$) en pacientes con deficiencia renal (de 85 a 140 min), lo que correspondía a un descenso del 30% en la depuración del plasma. La concentración de metabolitos en el plasma nunca excedió del 7% del fazadinio inalterado. Estos resultados sugieren que, en pacientes con deficiencia renal, la duración de acción del fazadinio será menos prolongada que la de otras drogas bloqueadoras neuromusculares no-depolarizadas. Una vía biliar adicional parece constituir la explicación posible de la rápida eliminación del fazadinio, aún en pacientes con deficiencia renal.

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RETROSPECTIVE ANALYSIS OF ANAESTHETICS RECEIVED BY PATIENTS BEFORE SUSCEPTIBILITY TO MALIGNANT HYPERPYREXIA WAS RECOGNIZED

P. J. HALSALL, P. A. CAIN AND F. R. ELLIS

SUMMARY

We have reviewed the anaesthetic histories of patients later found to be susceptible to malignant hyperpyrexia (MH). Many patients known to have this condition have been exposed to the known inducing agents previously, sometimes on more than one occasion. It is clear that insusceptibility to MH cannot be assumed from previous uneventful exposure to the known triggering agents and that all patients suspected of having inherited MH must be screened by *in vitro* muscle biopsy studies. No common factor could be found to explain this phenomenon.

Malignant hyperpyrexia (MH) is characterized by an inherited susceptibility to certain drugs used in anaesthesia which cause a rapid increase in body temperature, muscle contracture, acidosis and hyperkalaemia. However, this is not invariably the sequence of events when MH susceptible patients (MHS) are exposed to drugs known to induce the condition (Cain and Ellis, 1977) and many patients known to be MHS have had previous anaesthetics without any untoward effects. One study of previous anaesthetic exposure by Britt and Kalow (1970) reported 30 such patients, but no details were given other than that 21 patients had an increase in body temperature and nine did not.

The reason for the variable expression of the condition within an individual remains a mystery, although it is possible that there are "protective" factors such as concurrent drug therapy, as was suggested for continuous infusion of Althesin by Harrison (1973) or factors relating to the patient's physiological state, such as "stress", which are difficult to assess retrospectively. It was decided to review the anaesthetic histories of 100 patients referred to this unit who were subsequently investigated by muscle biopsy and found to be MHS.

METHODS

One hundred MHS patients were asked to complete a questionnaire. The group included probands with an undoubted history of a clinical MH episode confirmed by a positive halothane muscle contracture test (Ellis et al., 1978) and relatives of probands who were found to be MHS following investigation in this unit.

In the questionnaire patients were asked to indicate all previous exposures to anaesthetics, both local and general, giving the date, place, operation and names of professional attendants. Patients were asked for details of drug therapy, vaccinations, allergies or illnesses concurrent with the relevant anaesthetics. On receipt of this questionnaire the hospital or dentist was contacted by letter and asked for the following details:

(1) Date of anaesthetic.
(2) Duration of anaesthesia.
(3) Type of operation.
(4) All drugs used, including non-anaesthetic agents.
(5) Type of anaesthetic machine, circuit and vaporizer.
(6) Unusual reactions.

For the probands the anaesthetic details of the MH reaction were compiled for comparison with their previous anaesthetics.

RESULTS

Of the 100 questionnaires sent, 73 patients replied, of whom 22 were probands. For full details see table I.

Probands

Twenty patients received a total of 30 previous general anaesthetics. Meaningful details were available for only 13 anaesthetics. In these, halothane without suxamethonium was administered on seven occasions to five patients, suxamethonium to one

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TABLE I. *Overall numbers of anaesthetics (local and general) given to probands and relatives*

	Probands	Relatives
No. receiving general anaesthesia	20	38
No. general anaesthetics administered	30	62
No. receiving local anaesthesia	7	28
No. local anaesthetics administered	19	38

patient and halothane with suxamethonium to two patients (one of whom received this combination twice). The details of the general anaesthetics which included the MH inducing agents are shown in table II.

It can be seen from table II that i.v. induction agents were only used in three cases and premedication with agents other than anticholinergic drugs was used on five occasions. Hence, premedicants and i.v. induction agents were omitted in six anaesthetics.

A further eight patients had received 14 anaesthetics for which no details were available before an MH reaction. From the nature of the operation and date, the anaesthetic technique could be postulated. It is likely that five of these anaesthetics involved the use of halothane and for the remainder ether, vinesthene and ethyl chloride were probably used. In addition, two patients had received ether and one patient nitrous oxide and oxygen for dental extractions.

Many of the probands had undergone dental treatment with local anaesthesia, but detailed information was scanty. Seven patients received 19 local anaesthetics in which lignocaine was used five times and prilocaine once. Of the remaining local anaesthetics, cocaine, lignocaine and prilocaine were the agents involved.

These uneventful anaesthetics can be compared with the anaesthetics which, in the same patients, caused the episode of malignant hyperpyrexia (table III). In three of the eight anaesthetics both premedication and i.v. induction agents were omitted. Both the uneventful and the triggering anaesthetics involved children and young adults and the surgical operations were similar. Patient 282 had received three previous dental anaesthetics involving halothane and patient 139 had a dental halothane anaesthetic 8 years after his MH reaction without any untoward effect being noticed. The same patient also had an ether anaesthetic without any ill effect. However, during a previous anaesthetic patient 311 developed bradycardia and marked fasciculations causing opisthotonus after suxamethonium. Tracheal intubation was not difficult and the anaesthetic proceeded with 0.5% halothane with nitrous oxide with intermittent positive pressure ventilation for 1 h. The patient was noted to be pale and sweaty after pethidine premedication.

TABLE II. *Uneventful previous general anaesthesia in probands involving known MH trigger agents. TDP = tear duct probing; S = squint; H = hernia; D = dental; C = circumcision; T = tonsils; RTA = road traffic accident; P = plastic surgery to arm*

	Proband										
	94a	139	156	158a	204a	282	282	282	283a	311	311
Drug											
Atropine	×	×	×							×	
Hyoscine					×						×
Pethidine		×								×	
Papaveretum					×						×
Triclofos		×									
Pentobarbitone			×								
Thiopentone										×	×
Methohexitone					×						
Suxamethonium			×		×					×	×
Nitrous oxide	×	×	×	×	×	×	×	×	×	×	×
Halothane	×	×	×	×		×	×	×	×	×	×
Cyclopropane		×							×		
Pancuronium										×	×
Fentanyl										×	
Neostigmine+atropine										×	×
Antibiotics		×									
Operation	H	H	S	TDP	T	D	D	D	C	RTA	P
Age (yr)	5/12	3/12	1.5	1	1		(5–14)		1	18	

Suxamethonium was given during the subsequent anaesthetic without any comment about fasciculations, and anaesthesia was described as uneventful. The only difference between the two anaesthetics was the type of premedication, namely pethidine on the first occasion and papaveretum with hyoscine on the second occasion. However, when this patient developed MH during his third anaesthetic he was premedicated with papaveretum and hyoscine (table III) and suxamethonium was not used.

MHS relatives

Thirty-eight MHS patients (who have never developed MH) had been given a total of 62 general anaesthetics and sufficient details for further analysis were available for 24 of these. Halothane or suxamethonium, or both, had been administered on 17 occasions to 14 patients (table IV). In only four anaesthetics were premedicants and i.v. induction agents omitted, namely patients 101, 191, 195 and 258. Two patients, namely patients 94 and 195a, had received the inducing drugs on more than one occasion. In only two of the 17 anaesthetics were abnormal reactions noted. These were poor jaw relaxation (patient 133) and an increased heart rate and body temperature (patient 114). Inadequate jaw relaxation probably represented an abnormal reaction to suxamethonium, but during the same anaesthetic this patient subsequently received halothane without apparent ill effect. It is not recorded whether the proband of this particular family also developed jaw stiffness, since muscle rigidity is not an invariable response during MH. The increase in heart rate and body temperature occurring in patient 114 may have been a result of infection or toxaemia as surgery was performed for a perforated duodenal ulcer. However, this patient developed an increased temperature and heart rate following a subsequent vagotomy and pyloroplasty during which MH inducing agents were not used (table IV). Table IV also shows the details of seven anaesthetics in which the most common inducing agents (halothane and suxamethonium) were omitted.

TABLE III. *Anaesthesia causing MH. O = ptosis; S = squint; A = appendicectomy; F = fractured arm; P = plastic surgery to arm; Ad = adenoids*

	Proband							
	94a	139	156	158a	204a	282	283a	311
Drugs								
Atropine	×			×		×	×	
Hyoscine								×
Pethidine						×		
Papaveretum								×
Trimeprazine	×			×			×	
Thiopentone				×	×	×		×
Suxamethonium		×	×	×	×	×	×	×
Nitrous oxide	×		×	×	×	×	×	×
Halothane	×		×	×	×	×	×	×
Cyclopropane							×	
Curare				×				
Operation	O	O	S	O	R	A	Ad	P
Age (yr)	5	5.5	3	3	14	20	6	18

An additional 19 patients had received a total of 38 anaesthetics for which no details were available. However, it is probable that halothane had been administered six times, ethyl chloride once, ether once and vinesthene three times.

Twenty-eight MHS relatives underwent 38 local anaesthetics for dental, casualty and other minor operative procedures and obstetric extradurals. These included five lignocaine, three cocaine and two bupivacaine anaesthetics.

Nine of the 73 total patients were said to have allergies, namely two with hay fever, five to penicillin and two to unspecified metals. Four patients had received unspecified vaccinations before anaesthesia and eight patients were taking other drugs concurrently, namely diazepam, chlordiazepoxide, ampicillin, penicillin, streptomycin, indomethacin and sulphasalazine. Information about the type of anaesthetic machine, vaporizer and tubing was insufficient to allow meaningful comment.

DISCUSSION

Twenty-two MHS patients had received halothane or suxamethonium, or both, before recognition of MH susceptibility on 28 occasions. There was no obvious common factor which could have protected these patients from an MH reaction during previous anaesthetic exposure.

The effects of premedication and method of induction of anaesthesia have been implicated in the variable response patients or swine show on exposure to inducing agents (Harrison, 1973; Gatz, Kerr and Wingard, 1978) but this was not supported by our findings.

Premedication with sedatives presumably reduces anxiety and the associated catecholamine response. However, it is interesting to note that sedative premedication was omitted in 10 cases when an MH reaction did not occur, but this was not statistically significant compared with the premedication before

TABLE IV. *Uneventful general anaesthesia in relatives (final seven do not include MH-triggering agents). Antibiotics: A = ampicillin; P = penicillin; S = streptomycin. Other drugs: I = indomethacin. Operations: DU = perforated duodenal ulcer; V+P = vagotomy+pyloroplasty; M = menisectomy; VV = varicose veins; VH = vulval haematoma; ET = tympanoplasty; S = squint; A = appendix; D = dental; H = Hernia; Ad = adenoids; HE = haemorrhoidectomy; TL = tubal ligation; CS = Caesarean section OM = osteomyelitis; RPC = retained products of conception; TOP = termination of pregnancy*

	Probands																							
	14	94	94	101	114	131	133	143	158	183	191	195	195	195	258	276	294	27	56	114	143	183	206	276
Drugs																								
Hyoscine	×								×							×								×
Atropine		×	×			×	×			×				×			×	×		×	×	×	×	
Papaveretum	×	×	×						×							×	×							×
Morphine	×					×												×			×		×	
Pethidine		×			×	×		×		×			×	×			×	×		×		×		
Prochlorperazine								×	×															
Promethazine								×	×												×			
Trimeprazine							×						×											
Phenobarbitone			×						×															
Amylobarbitone			×																					
Perphenazine																	×							
Thiopentone	×	×	×		×	×	×	×	×		×					×	×	×		×	×		×	×
Methohexitone				×						×			×											
Suxamethonium	×		×				×			×	×		×	×		×	×							
Gallamine				×										×						×			×	
Pancuronium					×												×			×				
Curare	×																							
Levorphanol																					×			
Fentanyl											×										×			
Droperidol											×									×	×			
Phenoperidine																				×				
Halothane	×	×	×	×	×	×	×	×	×			×		×	×	×								
Vinesthene																			×					
Cyclopropane														×										
Trichloro-ethylene																						×		×
Nitrous oxide	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Neostigmine/atropine	×			×	×												×			×			×	
Ergotamine										×							×							×
Antibiotics and other drugs			A	P	PS																I			
Operation	V+P		VH	TL	DU	M	S	VV	HE	CS	D	D	Ad	H	D	ET	CS	OM	D	V+P	VV	RPC	A	TOP
Age (yr)	41		30	30	33	21	5	56	30	31	20	9	4	1	9	16	37	12	8	34	59	18	8	16

anaesthetics which resulted in MH. Of 50 patients referred to this unit as suspected cases of MH and subsequently shown to be MHS, 28 had received premedication or i.v. induction agents, or both, two patients had received neither and no information was available on the remaining patients. In addition, the anaesthetic we use for muscle biopsy for screening patients for MHS does not include premedication and induction takes place in the operating theatre, a combination likely to incur a significant amount of stress. Yet in no case (out of 321 biopsies) have any MH signs been noticed.

The significance of stress as a predisposing factor and the role of adrenergic stimulation has been reported by various workers (Hall, Lucke and Lister, 1977; Williams, 1977; Lucke et al., 1978), but the relative importance of sympathetic activity in the pathogenesis of MH has been refuted by Gronert, Milde and Theye (1977). Although this work was carried out in MH-susceptible pigs, stress may also be implicated in the aetiology of MH in humans. Wingard (1974, 1977) described the intolerance of MH patients to stresses such as heat, exercise, emotions and trauma. He describes an MH family in which there was a large number of sudden explained deaths not associated with anaesthesia. With a retrospective study it is impossible to assess a patient's "stress" at the time of an uneventful anaesthetic, and so no comparisons can be made between the uneventful anaesthetics and those resulting in MH.

The most commonly used local anaesthetic was lignocaine, which has been stated by Britt, Kwang and Endrenyi (1977) to be an MH triggering agent. However, lignocaine may not be as dangerous as previously suggested in view of the demonstration that extradural blockade with lignocaine protected against MH in pigs (Kerr, Wingard and Gatz, 1975). In dental practice systemic concentrations of lignocaine are very small, especially when it is combined with adrenaline.

Duration of exposure to the anaesthetic triggering agents may also have a role in the development of MH, as may the concentration of anaesthetic used. This may explain why dental-chair patients rarely develop MH. Patient 282 had three dental-chair general anaesthetics with halothane and patient 139 had a similar anaesthetic after the original MH episode without any recorded ill effect. Although little information was obtained from the questionnaires about the concentration of halothane used, we know from *in vitro* muscle studies that the majority of MHS muscle samples demonstrate a dose-dependent contracture with halothane.

This study demonstrates that previous uneventful exposure to MH-inducing agents cannot be taken to indicate insusceptibility to MH. It is therefore clear that all patients who are suspected of having inherited susceptibility to MH must be investigated by muscle biopsy with *in vitro* pharmacological testing, regardless of previous uneventful anaesthetic exposure. It is possible that the *in vitro* halothane challenge test may also produce a variable response. However, the muscle samples are isolated and uninfluenced by other physiological processes or drugs occurring in a patient undergoing anaesthesia. Wood (personal communication), when investigating single muscle fibre response to caffeine, found that a proportion of fibres taken from MHS muscle behaved normally. Similarly, we have occasionally found that several muscle samples taken from the same patient have quantitatively different reactions on exposure to halothane. The diagnosis of insusceptibility to MH (MHN) must be based on results obtained from multiple muscle samples.

Until a mechanism for the development of MH is elucidated, the occurrence of uneventful anaesthetics incorporating MH-inducing drugs must be viewed as an example of a within-patient variable expression of a complex pharmacogenetic disease.

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ANALYSE RETROSPECTIVE DES AGENTS ANESTHESIANTS RECUS PAR LES MALADES AVANT QUE L'ON RECONNAISSE LEUR SUSCEPTIBILITE A L'HYPERPYREXIE MALIGNE

RESUME

Nous avons passé en revue les antécédents anesthésiques de malades que l'on a trouvés par la suite, être réactifs à l'hyperpyréxie maligne (MH). De nombreux malades dont on savait qu'ils souffraient de cette maladie avaient auparavant été exposés à des agents connus pour la provoquer, et quelquefois même à plusieurs reprises. Il est évident que l'insensibilité à la MH ne peut pas être supposée du fait que toute exposition antérieure aux agents connus pour la déclencher n'a eu aucun effet et tous les malades que l'on soupçonne d'en avoir hérité doivent être dépistés par des études de biopsie du muscle effectuées *in vitro*. On n'a trouvé aucun facteur commun pouvant expliquer ce phénomène.

RETROSPEKTIVANALYSE VON NARKOSEMITTELN, DIE PATIENTEN ERHALTEN HATTEN, BEVOR DEREN ANFÄLLIGKEIT AUF MALIGNE HYPERPYREXIE ERKANNT WURDE

ZUSAMMENFASSUNG

Wir untersuchten die Narkosevorgeschichte von Patienten, deren Anfälligkeit auf maligne Hyperpyrexie (MH) später festgestellt worden war. Viele Patienten, deren diesbezüglicher Zustand bekannt war, sind früher den als auslösend bekannten Mitteln ausgesetzt worden, oft mehr als einmal. Es ist klar, dass eine Nicht-Anfälligkeit auf MH nicht daraus geschlossen werden kann, dass man den Patienten schon bei früheren Gelegenheiten den als auslösend bekannten Mitteln ohne Folgen ausgestetzt hat, und dass alle einer ererbten MH verdächtigen Patienten zuerst durch histologische Muskelstudien *in vitro* voruntersucht werden müssen. Zur Erklärung dieses Phänomens konnte kein gemeinsamer Faktor gefunden werden.

UN ANALISIS RETROSPECTIVO DE ANESTETICOS ADMINISTRADOS A PACIENTES ANTES DE COMPROBARSE SU SUSCEPTIBILIDAD A LA HIPERPIREXIA MALIGNA

SUMARIO

Examinamos los historiales anestéticos de pacientes reconocidos como susceptibles de hiperpirexia maligna (HM). Muchos pacientes en que se comprobó esta enfermedad, habían estado expuestos con anterioridad a agentes inducidores conocidos, algunas veces en más de una oportunidad. Está claro que no se puede dar por sentada la no-susceptibilidad a la HM a raíz de una exposición normal previa a agentes provocadores conocidos y que todos los pacientes supuestos haber heredado la HM deben ser controlados mediante estudios de biopsias musculares *in vitro*. No se encontró ningún factor común para explicar este fenómeno.

Br. J. Anaesth. (1979), **51**, 955

EFFECT OF DIAZEPAM AT THE NEUROMUSCULAR JUNCTION
A clinical study

E. G. BRADSHAW AND S. MADDISON

SUMMARY

In patients undergoing surgery under general anaesthesia diazepam 0.16 mg kg^{-1} had no effect on mechanical twitch height of the adductor pollicis muscle of the thumb when the ulnar nerve was stimulated at the wrist. The muscle responses were evoked by single, repeated supramaximal stimuli at 0.2 Hz and "train-of-four" stimulation at 2 Hz for 2 s. Diazepam 0.16 mg kg^{-1} had no effect on the depth or recovery of neuromuscular blockade produced by suxamethonium, tubocurarine, pancuronium, fazadinium or alcuronium.

An interaction between diazepam and neuromuscular blocking agents was suggested by Stovner and Endresen (1965), who believed that premedication with diazepam decreased the requirements for neuromuscular blockade. Although this was not confirmed, either in their later work (Stovner and Endresen, 1966) or by Hunter (1967), the controversy was re-opened by Feldman and Crawley (1970a, b) who found that diazepam potentiated the neuromuscular blockade produced by gallamine and enhanced the rate of recovery from a neuromuscular blockade by suxamethonium. Studies in animals and man (Dretchen, Ghoneim and Long, 1971) and in cats (Webb and Bradshaw, 1973) failed to demonstrate any action of diazepam at the neuromuscular junction in the clinical dose range. In the years following these studies a more sensitive and quantitative measurement of monitoring neuromuscular function by evoking short "trains-of-four" supramaximal stimuli to the ulnar nerve (Ali and Savarese, 1976; Lee and Katz, 1977) has been introduced.

The studies reported in this paper were undertaken to re-examine the controversial interaction of diazepam at the neuromuscular junction in man, using the train-of-four stimulation and single repeated supramaximal stimulation to evoke muscle responses.

METHODS

Men and women undergoing lower abdominal operations and surgery to the leg were studied. One arm was used for the i.v. administration of drugs and the other for recording contractions of the adductor pollicis longus muscle. All the patients gave informed consent and were premedicated with not more than

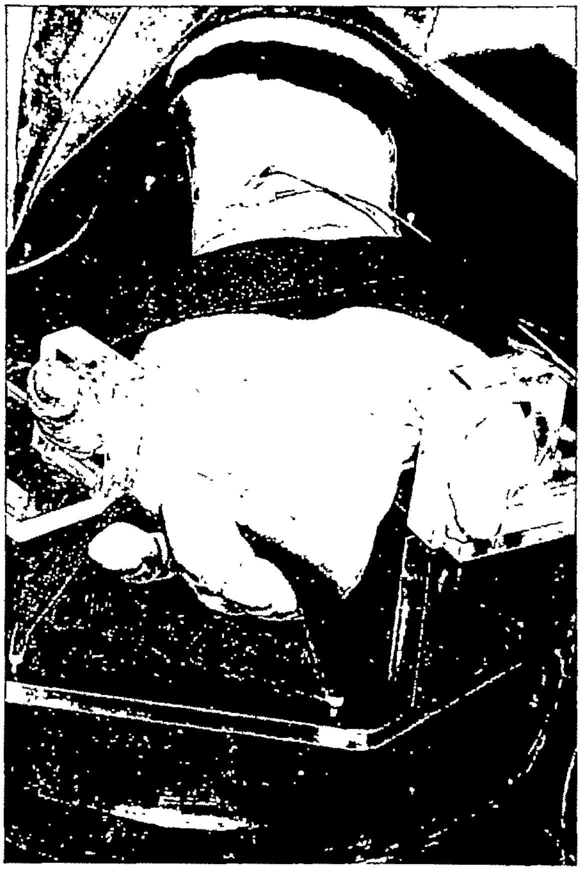

FIG. 1. The force transducer.

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diazepam 10 mg orally 1–2 h before operation. Anaesthesia was induced with a dose of thiopentone sufficient to abolish the eyelash reflex. Following the administration of 50–75 mg the trachea was intubated and anaesthesia was maintained subsequently with nitrous oxide 70% in oxygen. Fentanyl was administered in incremental doses of 50–100 μg i.v. to provide further analgesia. Ventilation was controlled with a tidal volume of 10 ml kg^{-1} and a respiratory rate of 14 b.p.m. delivered by a Blease or Manley respirator.

The patient's hand was positioned palm upwards on the Perspex base plate of a force transducer which was designed to limit changes in the position of the thumb while immobilizing the hand by constraining the little finger (fig. 1). The thumb was abducted to obtain a moderate resting tension of the adductor pollicis muscle as described by Ali and Savarese (1976). The plastic fittings could be interchanged to allow use with either hand. Four electrical strain gauges were mounted on the steel strip protected by a Perspex cover plate. Bending the steel strip resulted in compression of gauges (1) and (2) and extension of strain gauges (3) and (4) (fig. 2). The four gauges were connected in a Wheatstone bridge circuit in such a way as to eliminate the effects of direct loads, to magnify bending strains by a factor of 4 and to compensate for changes in resistance as a result of temperature variation. A potentiometer was added to correct imbalance from slightly different gauge resistances. The force transducer was connected to a pre-amplifier (3552) and a recorder (Ormed MX212). The apparatus was calibrated by weights ranging from 5 g to 2 kg applied in the direction shown in figure 2. The calibration lines did not differ significantly from linearity; for example, range 100 ($r = 0.999$) (fig. 3).

Following recovery from suxamethonium, the ulnar nerve was stimulated at the wrist using skin (Medelec) or subcutaneous needle electrodes (Grass) connected to a nerve stimulator (Grass S48).

The ulnar nerve was stimulated supramaximally with rectangular pulses at a frequency of 0.2 Hz. Control readings of single twitch and train-of-four fade were made. The latter were trains-of-four supramaximal stimuli applied for 2 s every 10 s. Then the single twitch response was recorded while neuromuscular blocking drugs were injected via an i.v. infusion to the opposite arm. The following neuromuscular blocking agents were investigated: pancuronium, tubocurarine, alcuronium, fazadinium and suxamethonium. Incremental doses of one of these were administered to obtain blockade approximately 50% of control. When maximum blockade had been achieved, as observed by both single twitch and train-of-four stimulation, the patient received either diazepam 0.16 mg kg^{-1} i.v. or equivalent volumes of saline as a control. Continuous recordings of single twitches interspersed at 3-min intervals with trains-of-four stimuli were made until recovery from the blockade or the requirement, on surgical grounds, for greater relaxation.

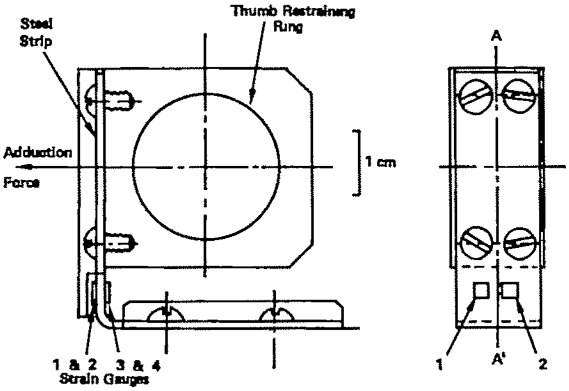

FIG. 2. The arrangement of the transducer and strain gauges.

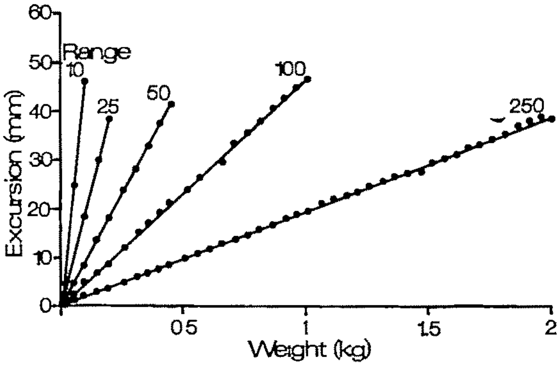

FIG. 3. The calibration of the force transducer.

The results of the single twitch response were expressed as a percentage of pre-drug control tensions, and the train-of-four stimulation ratio was measured as the height of the fourth to the first twitch expressed as a percentage. Statistical significance was assessed using the Mann–Whitney *U* test.

RESULTS

The intravenous administration of diazepam alone had no effect on either the single twitch or the train-of-four stimulation.

TABLE I. *Mean dose of muscle relaxant and mean time required to produce approximately 50% neuromuscular blockade as measured by train-of-four stimulation and single twitch. Control measurements before diazepam. Results are expressed as mean and range. C = control experiments; T = experiments when diazepam was administered after the above results were obtained. Not less than 10 patients studied for each value*

Drug		Dose (mg)	Time to maximum blockade(s)	
			Train-of-four ratio	Single twitch
Tubocurarine	C	8.6 (3–12)	286 (188–334)	278 (180–386)
	T	10.0 (5–14)	296 (249–360)	273 (240–305)
Fazadinium	C	22.5 (15–30)	243 (183–305)	242.5 (180–300)
	T	20.63 (15–30)	214 (60–260)	206 (60–252)
Pancuronium	C	2.0 (1–3)	335 (302–363)	312 (288–360)
	T	2.10 (1.5–3.0)	285 (194–426)	276 (180–420)
Alcuronium	C	6.25 (5–7.5)	243 (140–323)	194 (180–200)
	T	5.13 (4.5–6)	271 (170–310)	227 (180–270)

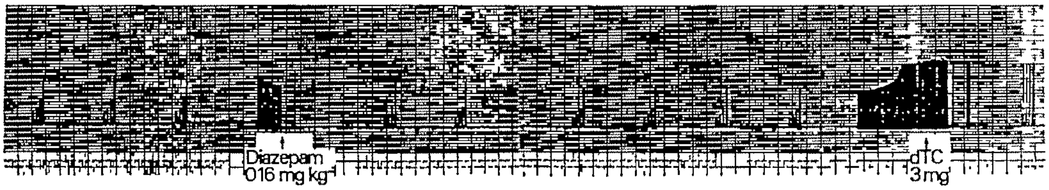

FIG. 4. The effect of diazepam 0.16 mg kg^{-1} i.v. on the neuromuscular blockade produced by tubocurarine 3 mg i.v. (dTC) on the adductor pollicis muscle of the anaesthetized human male. Single stimuli were applied to the ulnar nerve at a frequency of 0.2 Hz and supramaximal voltage, duration 2 ms. The train-of-four stimulation was applied at 2 Hz for 2 s and repeated every 10 s. The trace reads from right to left. The chart speed for the single twitches was one large division (5 mm) = 50 s and for train-of-four one large division = 2 s.

TABLE II. *Interaction between diazepam 0.16 mg kg^{-1} and neuromuscular blocking agents in man; inhibition of twitch height. T = patients given diazepam; C = patients not given diazepam; twitch height measured at time corresponding to T*

Drug		% Inhibition of twitch height (mean ± SEM)		
		At time of maximum block, before diazepam	3 min after diazepam	No diazepam (control)
Tubocurarine	T	47.3 ± 5.7	49.9 ± 5.9	
	C	46.2 ± 2.2		42.5 ± 3.8
Alcuronium	T	50.0 ± 6.4	43.6 ± 7.7	
	C	55.8 ± 13.3		53.75 ± 11.5
Pancuronium	T	55.6 ± 8.6	53.6 ± 6.9	
	C	68.2 ± 10.7		62.8 ± 5.5
Fazadinium	T	38.0 ± 7.8	35.2 ± 8.6	
	C	71.4 ± 6.9		54.6 ± 8.3

The doses (mg) of the neuromuscular blocking agents are shown in table I, with the time to maximum neuromuscular blockade measured with train-of-four stimulation ratios or single twitch. This shows that in both control experiments and experiments in which diazepam was given after the development of maximum blockade there was no significant difference between these values and, therefore, the groups were comparable. The greater sensitivity of the train-of-four stimulation ratio, expressed as a percentage for

TABLE III. *Interaction between diazepam* 0.16 *mg kg*$^{-1}$ *and neuromuscular blocking agents in man; train-of-four stimulation ratio. T, C as table II*

Drug		Train-of-four stimulation ratio (mean ± SEM)			
		Control	At time of maximum block, before diazepam	3 min after diazepam	No diazepam (control)
Tubocurarine	T	99.33 ± 0.66	20.12 ± 4.27	24.37 ± 4.40	
	C	96.30 ± 1.43	32.76 ± 5.25		32.90 ± 6.91
Alcuronium	T	96.05 ± 2.29	21.35 ± 4.09	25.78 ± 3.7	
	C	98.35 ± 0.96	29.88 ± 8.29		23.6 ± 8.08
Pancuronium	T	84.65 ± 12.15	13.18 ± 2.53	23.52 ± 4.55	
	C	84.28 ± 13.99	16.54 ± 4.05		18.48 ± 3.67
Fazadinium	T	106.20 ± 3.82	29.09 ± 9.66	27.93 ± 6.28	
	C	96.00 ± 4.00	7.95 ± 2.04		14.23 ± 10.35

TABLE IV. *Recovery rate of train-of-four stimulation and single twitch expressed as % change per minute (mean and range) following competitive muscle relaxants alone (C) and in the presence of diazepam* 0.16 *mg kg*$^{-1}$ *(T). No significant differences were detected between C and T groups using the Mann–Whitney U test*

Drug		Train-of-four ratio	Single twitch
Tubocurarine	C	2.45 (1.17–3.49)	2.75 (0.00–5.37)
	T	1.7 (0.35–4.40)	3.76 (2.00–4.88)
Fazadinium	C	2.61 (0.00–4.54)	5.09 (0.00–11.11)
	T	2.86 (1.04–7.20)	7.15 (5.00–8.33)
Pancuronium	C	2.36 (0.84–4.13)	2.30 (0.00–4.16)
	T	2.88 (1.67–4.85)	4.63 (2.10–7.32)
Alcuronium	C	2.88 (0.00–7.92)	4.35 (2.30–7.9)
	T	4.09 (2.25–6.52)	3.28 (1.68–4.54)

neuromuscular competence, is shown in table III; it was reduced by 70–90%. In the same patients only 40–70% inhibition of twitch height was observed.

The lack of interaction between diazepam and the competitive neuromuscular blocking agents is shown in figure 4 (diazepam was administered following a prior injection of tubocurarine). Compared with control readings, diazepam did not significantly increase the inhibition of twitch height produced by tubocurarine, alcuronium, fazadinium and pancuronium (table II). Similarly, diazepam had no effect on the marked reduction of the train-of-four stimulation ratio produced by the myoneural blocking drugs (table III). In table IV the results have been expressed for the rate of recovery as measured by the train-of-four ratio and single twitch. Some patients showed no recovery of blockade during the investigation. No significant differences could be detected between control and diazepam-treated patients.

The interaction of diazepam and suxamethonium administered by a single bolus injection or a continuous infusion was studied. Only the single twitch was recorded, as train-of-four stimulation ratio is not applicable to depolarizing blockade. Although quantification was difficult, no interaction between diazepam and suxamethonium was seen (fig. 5).

DISCUSSION

There was no action of diazepam 0.16 mg kg^{-1} at the neuromuscular junction and there was no evidence of any interaction between diazepam and the neuromuscular blocking agents tubocurarine, pancuronium, fazadinium, alcuronium or suxamethonium in humans. These results conflict with those of Feldman and Crawley (1970a, b), who found that diazepam potentiated the duration of the neuromuscular blockade produced by gallamine and enhanced the recovery of blockade from suxamethonium. Since the dose range of diazepam in

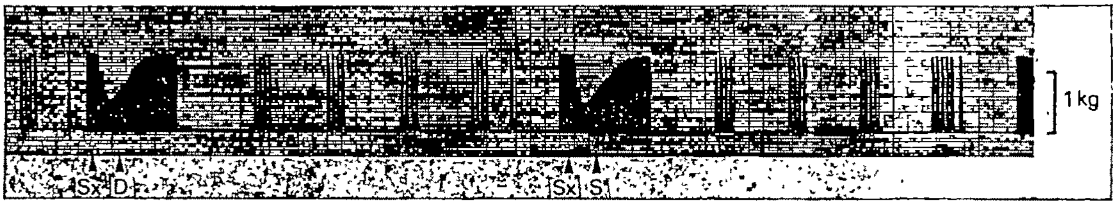

FIG. 5. The effect of diazepam 0.16 mg kg^{-1} i.v. (D) and equivalent volumes of saline (S) on the neuromuscular blockade produced by suxamethonium 10 mg i.v. (Sx) in the adductor pollicis muscle of the anaesthetized human male. Single stimuli were applied to the ulnar nerve at the wrist at a frequency of 0.2 Hz and supramaximal voltage, duration 2 ms. The train-of-four stimulation was applied at 2 Hz for 2 s and repeated every 10 s. The chart speed for the single twitches was one large division (5 mm) = 50 s and for train-of-four one large division = 2 s.

these studies is comparable, the differences in the findings is probably a result of experimental design. Feldman and Crawley (1970a, b) obtained a control response to the myoneural blocking agent and then injected diazepam before a second dose of the muscle relaxant in the same patient. In our study diazepam was given at the maximum blockade. Control responses and test studies with diazepam were performed in separate patients to avoid artefacts resulting from cumulation of muscle relaxants. This was demonstrated in the experiments in cats by Webb and Bradshaw (1973), in which a cumulative effect was evident even when more than 2 h had elapsed between injections of gallamine and tubocurarine. Although a neuromuscular junction may have recovered fully from blockade with respect to twitch height and tetanic responses, significant quantities of the muscle relaxants may remain in non-specific binding sites. Thus, a second dose of drug may be bound less and so have a greater action at the neuromuscular junction. In the study by Feldman and Crawley (1970a, b) the results from only four patients who received three different doses of gallamine were reported. Therefore, no statistical analysis of the results was possible and no follow-up study was undertaken.

The results of our studies are supported by Dretchen, Ghoneim and Long (1971), who showed that diazepam in doses as great as 1.2 mg kg^{-1} had no effect on the recovery rate of blockade produced by tubocurarine, gallamine or decamethonium in humans.

Animal experiments have not revealed any action of diazepam in therapeutic doses at the neuromuscular junction. Experiments on the cat anterior tibialis preparation (Hamilton, 1967; Crankshaw and Raper, 1968) showed that diazepam abolished the polysynaptic reflex contractions in a concentration that had no effect on the non-reflexly evoked contractions or on the refractory period of indirectly stimulated muscle.

Similar results were obtained by Southgate and Wilson (1971). Dretchen, Ghoneim and Long (1971) could demonstrate only blockade of the contractions of cat and dog sciatic nerve–anterior tibialis preparations at high concentrations of diazepam injected i.a. These authors suggested that at these concentrations diazepam had a direct depressant effect on the muscle.

Therefore, as such great concentrations of diazepam are required to produce an effect at the neuromuscular junction, this cannot be the main site of action of the relaxant effect. The probable sites of action remain the supra-spinal structures, such as the reticular activating system, and polysynaptic pathways in the spinal cord (Randall et al., 1961). A central site of action would explain the effectiveness of diazepam in the treatment of tetanus (Shershin and Katz, 1964; Femi-Pearse, 1966; Hendrickse and Sherman, 1966; Dundee and Haslett, 1970), for controlling muscle rigidity and spasticity in neurological disorders (Olafson, Mulder and Howard, 1964; Nathan, 1970) or in improving patient acceptability of positive pressure ventilation (Bozza-Marrubini and Selenati, 1973).

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EFFET DU DIAZEPAM A LA JUNCTION NEUROMUSCULAIRE

Etude clinique

RESUME

Chez des malades soumis à une intervention chirurgicale effectuée sous anesthésie générale, le diazépam administré à raison de 0,16 mg kg^{-1} n'a aucun effet sur l'intensité de la crispation mécanique du muscle adducteur du pouce, lorsqu'on excite le nerf ulnaire au poignet. Les réactions du muscle ont été évoquées par des stimulations supramaximales isolées et répétées à 0,2 Hz et par des stimulations en "chaîne de quatre" à 2 Hz pendant 2 s. Le diazépam, administré à raison de 0,16 mg kg^{-1}, n'a eu aucun effet sur la profondeur ou la récupération du blocage neuromusculaire produit par le suxaméthonium, la tubocurarine, le pancuronium, le fazadinium ou l'alcuronium.

WIRKUNG VON DIAZEPAM AN DER NEUROMUSKULÄREN VERBINDUNG

Eine Klinische Studie

ZUSAMMENFASSUNG

Bei Patienten, die unter allgemeiner Narkose operiert wurden, hatten 0,16 mg kg^{-1} Diazepam auf die mechanische Zuckungshohe des Adductor pollicis-Muskels im Daumen, wenn der Ulnarnerv am Handgelenk stimuliert wurde. Die Muskelreaktionen wurden durch einzelne, supermaximale Stimuli bei 0,2 Hz und durch Vierer-Stimuli bei 2 Hz für 2 Sekunden hervorgerufen. Eine Dosis von 0,16 mg kg^{-1} Diazepam hatte keine Auswirkung auf Tiefe oder Erholung aus der neuromuskulären Blockierung, die durch Suxamethonium, Tubocurarin, Pancuronium, Fazadinium oder Alcuronium bewirkt worden war.

EFECTO DEL DIAZEPAM EN JUNCIONES NEUROMUSCULARES

Un estudio clínico

SUMARIO

Cuando se estimuló en la muñeca al nervio ulnar de pacientes bajo anestesia general sometidos a operaciones quirúrgicas a los cuales se había administrado 0,16 mg kg^{-1} de diazepam, no se registró variación alguna en el alto de la contracción mecánica del músculo aductor del pulgar. Las respuestas del músculo fueron provocadas por estímulos supramaximales individuales en 0,2 Hz y con estimulación en serie de cuatro, en 2 Hz durante 2 s. El diazepam 0,16 mg kg^{-1}, no hubo variación en la intensidad o la recuperación del bloqueo neuromuscular producido por el suxamentonio, la tubocurarina, el pancuronio, el fazadinio o el alcuronio.

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NEFOPAM IN POSTOPERATIVE PAIN

G. PHILLIPS AND M. D. A. VICKERS

SUMMARY

Three comparable groups of surgical patients were given nefopam 0.2 mg kg^{-1} or 0.4 mg kg^{-1} or morphine 0.15 mg kg^{-1} for pain relief after operation. Nefopam 0.4 mg kg^{-1} was equi-analgesic with morphine 0.15 mg kg^{-1} and produced no obvious cardiovascular or respiratory side-effects.

Nefopam hydrochloride is a new non-narcotic analgesic agent unrelated pharmacologically to any known analgesic drug. Its analgesic effects have been demonstrated by Cohen (1974), Gassel and others (1976) and Workmon and Winter (1974). Gasser and Belville (1975) found no evidence of respiratory depression when nefopam was administered parenterally in therapeutic doses. Indeed, it appeared to possess central nervous system stimulant effects (Re, 1975). Sunshine and Laska (1975) and Beaver and Feise (1977) have shown that nefopam 20 mg is equi-analgesic with morphine 7–12 mg. A double-blind clinical trial was devised to assess the efficacy of nefopam given parenterally at two doses for pain after operation and to compare it with morphine, to determine the equi-analgesic dose of morphine and nefopam.

PATIENTS AND METHODS

Seventy-six patients of either sex, between the ages of 18 and 70 yr (weight 50–80 kg), were allocated randomly to one of three trial groups. Any patient with medical disease was excluded, as were pregnant or lactating women. Written, informed consent was obtained from each patient before study.

The patients were premedicated with an opiate or a tranquillizing drug, with or without the addition of atropine. Anaesthesia was induced with thiopentone, usually followed by suxamethonium, and maintained with nitrous oxide in oxygen, supplemented with halothane or neuroleptanalgesia (fentanyl or phenoperidine with droperidol). A myoneural blocking drug was given to facilitate artificial ventilation of the lungs.

Each patient was given a single dose of the test analgesic within 24 h of when he or she complained of moderate to severe pain, provided that at least 4 h had elapsed since any previous administration of analgesic.

The doses used were morphine 0.15 mg kg^{-1} and nefopam 0.2 and 0.4 mg kg^{-1}. The patient's weight was measured to the nearest 5 kg and the drugs administered in a volume of 0.1 ml/5 kg i.m. The drugs were dispensed in identical ampoules and neither patient nor observer was aware of which drug had been given.

The patients were interviewed throughout by the same observer (G. P.), who recorded the pain as absent, mild, moderate or severe, and asked about any side-effects. Pain relief was assessed before the test dose, at 20, 40 and 60 min after administration, and again after 2, 3, 4, 5 and 6 h. In addition to asking about specific symptoms, the patients were asked on each occasion "How do you feel?" in an attempt to elicit other symptoms. The side-effects were graded as mild, moderate or severe.

Any patient who had inadequate pain relief within 3 h of the test injection received supplementary analgesics and was withdrawn from the trial. If the pain was relieved initially but returned more than 3 h later, the analgesic drug prescribed by the surgical team for use after operation was given, but pain intensity and assessments of relief were taken as being at this level for the remainder of the trial.

Twenty-six patients received morphine sulphate 0.15 mg kg^{-1}, 25 received nefopam hydrochloride 0.2 mg kg^{-1} and 25 nefopam hydrochloride 0.4 mg kg^{-1}. One patient who received morphine on entering the study required further analgesics at 1 h and at 5 h and was withdrawn from the trial. Only the data from the remaining 75 patients were analysed. The patient responses were scored as 0–3, according to the

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severity of the pain, 0 indicating no pain and 3 indicating severe pain.

The following indices were derived:

Pain intensity score—the mean value at each assessment time

Pain intensity difference—the mean initial pain score minus the mean pain intensity score at each time

Sum of pain intensity difference score—the sum of the pain intensity difference scores weighted according to the time intervals between assessments.

RESULTS

The groups were comparable in respect of age and sex (table I) and the operations performed (table II). The mean initial pain intensity scores for the three groups ranged from 2.36 to 2.56 (table III), and these differences were not statistically significant. The pain intensity, pain intensity difference and summated pain intensity difference scores are shown in table III. The pain intensity and pain intensity difference scores are displayed in figures 1 and 2. The responses to nefopam 0.4 mg kg^{-1} and morphine 0.15 mg kg^{-1} were consistently greater than those to nefopam 0.2 mg kg^{-1}. However, these differences only became statistically significant after 2 h. This appeared to result from a shorter duration of action of the nefopam. This was seen also with the larger dose of nefopam and is reflected in the slightly smaller sum of pain intensity differences for nefopam 0.4 mg kg^{-1} compared with morphine 0.15 mg kg^{-1}.

TABLE I. *Details of patients studied. (Ranges in parentheses)*

	Nefopam hydrochloride		Morphine sulphate
	0.2 mg kg^{-1}	0.4 mg kg^{-1}	0.15 mg kg^{-1}
Mean age (yr)	52 (27–67)	54 (22–69)	51 (21–70)
Weight (kg)	65 (50–80)	66 (49–80)	65 (50–82)
Height (cm)	167 (152–183)	167 (152–185)	168 (152–188)
Sex			
Male	11	14	13
Female	14	11	12
Race			
European	23	24	23
Asian	2	1	2
Initial pain intensities			
Severe	11	9	14
Moderate	14	16	11

TABLE II. *Surgical procedures undergone by patients in the study*

	Nefopam hydrochloride		Morphine sulphate	
Operation	0.2 mg kg^{-1}	0.4 mg kg^{-1}	0.15 mg kg^{-1}	Total
Cholecystectomy	12	10	7	29
Vagotomy + pyloroplasty	4	3	4	11
Gastrectomy	2	2	4	8
Appendicectomy	2	1	2	5
Nephrectomy	1	1	1	3
Closure of colostomy		1	2	3
Bowel resection	2	3	3	8
Gastro-enterostomy	1		1	2
Ventral hernia repair	1			1
Pan-procto-colectomy		1		1
Pancreatico-duodenostomy		1		1
Laparotomy			1	1
Lumbar sympathectomy		2		2
Total	25	25	25	75

TABLE III. *Pain intensities (PI), pain intensity differences (PID) and weighted sum of pain intensity differences (SPID) (Mean ± SEM; $n = 25$). Significantly different from nefopam* $0.2\ mg\ kg^{-1}$: $^{*}P<0.05$; $^{**}P<0.01$

Index	Observation period	Nefopam hydrochloride		Morphine sulphate
		$0.2\ \text{mg kg}^{-1}$	$0.4\ \text{mg kg}^{-1}$	$0.15\ \text{mg kg}^{-1}$
PI	Baseline	2.44±0.10*	2.36±0.99*	2.56±0.10*
	20 min	1.48±0.10	1.20±0.08	1.40±0.10
	40 min	1.08±0.08	0.92±0.09	0.96±0.09
	60 min	0.96±0.10	0.64±0.11	0.80±0.10
	90 min	0.92±0.11	0.60±0.11	0.76±0.08
	2 h	0.92±0.09	0.64±0.13	0.76±0.08
	3 h	1.20±0.10	0.80±0.13*	0.84±0.09*
	4 h	1.44±0.11	1.00±0.14*	1.16±0.12
	5 h	1.76±0.12	1.32±0.12*	1.40±0.11*
	6 h	1.92±0.09	1.36±0.14	1.60±0.13
PID	20 min	0.96±0.06	1.16±0.09	1.16±0.07
	40 min	1.36±0.09	1.44±0.14	1.60±0.10
	60 min	1.48±0.11	1.72±0.13	1.76±0.12
	90 min	1.52±0.11	1.76±0.14	1.80±0.11
	2 h	1.52±0.11	1.72±0.14	1.80±0.11
	3 h	1.24±0.10	1.56±0.16	1.72±0.12**
	4 h	1.00±0.13	1.36±0.19	1.40±0.15
	5 h	0.68±0.14	1.04±0.17	1.16±0.15*
	6 h	0.52±0.11	1.00±0.16*	0.96±0.15*
SPID		6.21±0.52	8.13±0.85	8.51±0.71

TABLE IV. *Summary of possible drug-related side-effects*

	Treatment groups		
	Nefopam $0.2\ \text{mg kg}^{-1}$	Nefopam $0.4\ \text{mg kg}^{-1}$	Morphine $0.15\ \text{mg kg}^{-1}$
Number of patients	25	25	25
Number of patients with side-effects	24	23	20
Total number of side-effects	43	52	41
Nature and frequency of side-effects			
Drowsiness	17	7	19
Dizziness/lightheadedness	5	4	6
Headache	1	1	
Agitation		1	
Euphoria	1	4	1
Malaise	1	1	1
Sweating	15	16	3
Fever		3	1
Flushing	1	5	
Tachycardia		1	
Faintness	1		
Blurred vision		2	
Deafness			1
Dry mouth	1	1	1
Nausea		3	5
Vomiting		1	2
Heartburn		1	1
Micturition difficulty	1	1	
Itching		1	

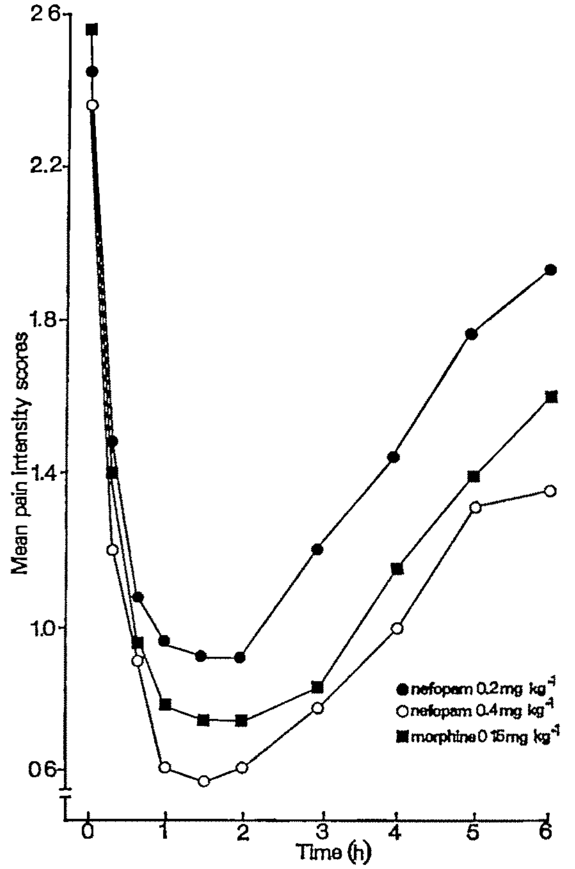

FIG. 1. Mean pain intensity score (3 = severe, 2 = moderate, 1 = slight) in patients treated with a single dose of nefopam hydrochloride or morphine sulphate during a 6-h period of observation. Each point represents the mean result for 25 patients.

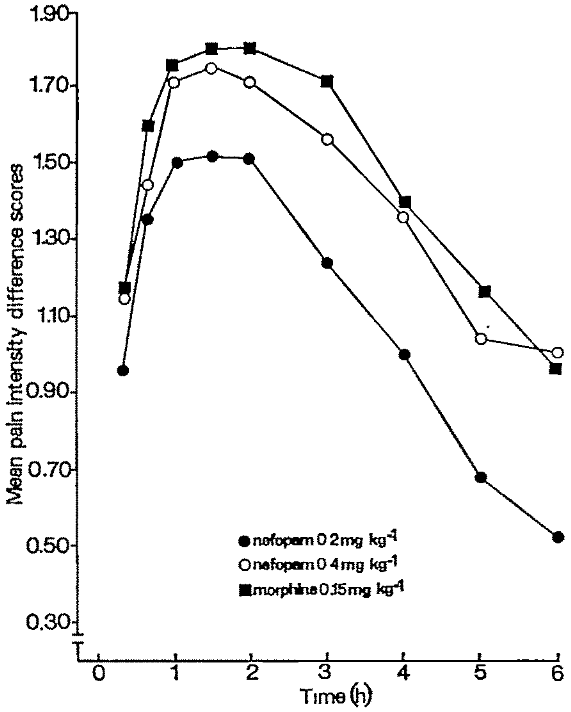

FIG. 2. Mean pain intensity difference scores in patients treated with a single dose of nefopam hydrochloride or morphine sulphate. Scores are calculated by subtracting the mean pain intensity score for each observation point from the pain intensity at zero hour. Each point represents the mean result for 25 patients.

The most common side-effect was drowsiness, which occurred in 70% of patients who received morphine, and 68% of those given low-dose nefopam (table IV). The frequency of drowsiness in patients given the larger dose of nefopam was significantly less ($P < 0.01$).

The most striking side-effect of nefopam was sweating, which occurred in 62% of patients. It was usually transient, starting 20–30 min after administration of the drug, and lasting 20–30 min. The frequency of all side-effects was greatest in the group receiving high-dose nefopam; four patients in this group reported sensations of euphoria.

DISCUSSION

The methods employed for assessing pain relief in this study were based on those of Houde, Wallenstein and Rogers (1960). Apart from three patients who underwent nephrectomy, all the patients in the trial underwent abdominal surgery so that the nature and severity of the pain which followed operation was standardized to some extent (Parkhouse, Lambrechts and Simpson, 1961).

The pain scores for morphine found in this trial agree with those quoted by Sunshine and Laska (1975) and Beaver and Feise (1977). The larger dose of nefopam produced an analgesia curve similar to that of morphine in terms of onset of action, peak relief of pain and duration of action; statistical analysis was unable to differentiate between the two. The degree of analgesia and duration of action of the smaller dose of nefopam was less than that afforded by the other drug regimes and this difference was statistically significant at all times after 3 h. The results indicate that nefopam 20 mg is therapeutically equivalent to morphine 7.5 mg when the drugs are given i.m. This compares with two previous series in which nefopam 20 mg has been shown to be equi-analgesic with morphine 12 mg and 7 mg respectively (Sunshine and Laska, 1975; Beaver and Feise, 1977).

There was a high frequency of drowsiness, though the larger dose of nefopam produced less, presumably because of the central nervous system stimulant effect of the drug (Re, 1975). Sweating was the most severe side-effect of nefopam, but this was usually transient. The occurrence of euphoria in a proportion of patients receiving the large dose of nefopam is noteworthy. This drug has been noted to have some anti-depressant effect, although previous studies using an oral preparation which was administered to volunteers over a 90-day period failed to show any evidence of habituation (Klotz, 1974).

Nefopam hydrochloride appears to be an effective analgesic agent in the treatment of moderate to severe pain after operation, and is free of serious cardiovascular or respiratory side-effects. Nefopam 20 mg was found to be approximately equi-potent with morphine sulphate 7.5 mg.

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LE NEFOPAM CONTRE LA DOULEUR POST-OPERATOIRE

RESUME

On a administré à trois groupes comparables d'opérés du néfopam à raison de 0,2 mg kg^{-1} ou de 0,4 mg kg^{-1} ou encore de la morphine à raison de 0,15 mg kg^{-1} pour soulager la douleur post-opératoire. Le néfopam à raison de 0,4 mg kg^{-1} a été équi-analgésique à la morphine administrée à raison de 0,15 mg kg^{-1} et n'a produit aucun effet secondaire respiratoire ou cardiovasculaire évident.

NEFOPAM FÜR POSTOPERATIVE SCHMERZEN

ZUSAMMENFASSUNG

Drei vergleichbare operative Patienten erhielten entweder 0,2 mg kg^{-1} oder 0,4 mg kg^{-1} Nefopam, oder 0,15 mg kg^{-1} Morphium zur Schmerzlinderung nach Operationen. Eine Dosis von 0,4 mg kg^{-1} Nefopam hatte dieselbe Wirkung wie 0,15 mg kg^{-1} Morphium und bewirkte keine offensichtlichen kardiovaskulären oder respiratorischen Nebenerscheinungen.

NEOFAM EN DOLORES POSTOPERATORIOS

SUMARIO

Para aliviar los dolores postoperatorios, se administró a tres grupos de pacientes de cirujía comparables 0,2 mg kg^{-1} ó 0,4 mg kg^{-1} de neofam ó 0,15 mg kg^{-1} de morfina. Se comprobó que el poder analgésico de 0,4 mg kg^{-1} de neofam era igual al de 0,15 mg kg^{-1} de morfina y que no dió lugar a efectos respiratorios o cardiovasculares secundarios obvios.

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CIMETIDINE IN THE PREVENTION OF THE PULMONARY ACID ASPIRATION (MENDELSON'S) SYNDROME

G. DOBB, M. J. JORDAN AND J. G. WILLIAMS

SUMMARY

Cimetidine 200 mg was given i.v. 1 h before induction of anaesthesia to 20 patients about to undergo emergency surgery. There was an increase in pH of gastric aspirate in all patients ($P < 0.001$) and in 80% pH was greater than 2.5 units at the time of induction of anaesthesia. The pH of gastric aspirate continued to increase after induction of anaesthesia and was greater than 4 units in all patients at the time of tracheal extubation and in the early recovery period.

Pulmonary acid aspiration (Mendelson's) syndrome is responsible for a considerable proportion of the deaths associated with anaesthesia (Morton and Wylie, 1951; Edwards et al., 1956; Clifton and Hotten, 1963; Dinnick, 1964; Report, 1970–72) and has been recognized as a major hazard in the practice of emergency anaesthesia (Hall, 1940; Mendelson, 1946; Morton and Wylie, 1951). Experimental work in animals suggests that pulmonary damage is greatest when fluids with pH less than 2.5 units are aspirated (Teabeaut, 1952; Taylor and Pryse-Davies, 1966). The risk of the pulmonary acid aspiration syndrome may be reduced therefore by increasing the pH of gastric contents to more than 2.5 before induction of anaesthesia.

Cimetidine, a specific histamine H_2 receptor antagonist, reduces gastric acid secretion (Burland et al., 1975), but has little effect on the tone of the lower oesophageal sphincter (Bailey et al., 1976; Carter et al., 1977) or the rate of gastric emptying (Heading et al., 1977). This study was designed to investigate the effectiveness of cimetidine in reducing the acidity of stomach contents in patients about to undergo emergency surgery.

PATIENTS AND METHODS

Twenty patients (17 male, three female; mean age 44 yr, range 16–73 yr) were investigated. All were undergoing emergency surgery (table I) and all could be expected to have a "full stomach" according to the criteria suggested by Morton and Wylie (1951). No premedication was given (although three patients received as much as 100 mg of pethidine for analgesia).

One hour before surgery a 16-f.g. nasogastric tube was passed and up to 10 ml of stomach content aspirated. Cimetidine 200 mg was then given i.v. Further aliquots of 5–10 ml of gastric aspirate were removed at 15-min intervals. At the fifth aspiration, immediately before induction, the stomach was emptied as completely as possible. After induction of anaesthesia aspiration was repeated every 15 min until approximately 1 h after completion of surgery.

After pre-oxygenation of the patient, anaesthesia was induced with a predetermined dose of thiopentone followed immediately by suxamethonium 100 mg to facilitate orotracheal intubation. Maintenance of anaesthesia was determined by the nature of the surgery being performed and the condition of each patient, and was not standardized.

pH of the samples was measured within 12 h using a Radiometer TTT2 pH electrode and meter. The equipment was calibrated against standard buffers of pH 4, 7 and 9 units.

The results were analysed statistically using a paired *t* test.

The study was approved by the hospital ethics committees and all patients gave informed consent.

RESULTS

pH of gastric aspirate before administration oi cimetidine and before induction of anaesthesia is shown in table I. In 13 patients pH was less than 2.5 before receiving cimetidine. One hour after cimetidine only four patients still had a gastric aspirate pH of less than 2.5, although in these four pH was increasing.

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TABLE I. *Details of patients and the change in intragastric pH before induction of anaesthesia. *Received up to 100 mg of pethidine*

Patient no.	Age (yr)	Sex	Surgical condition	pH (units) before	
				Cimetidine	Induction
1*	25	M	Small bowel obstruction	1.2	7.7
2*	24	M	Torsion of testis	1.8	2.9
3	23	M	Stab wound	5.1	6.9
4	16	M	Perforated appendix	2.4	3.4
5	65	F	Small bowel obstruction	5.3	6.8
6	61	M	Compound Pott's fracture	1.9	3.8
7	61	M	Perforated gastric ulcer	1.5	2.3
8	70	F	Chylous ascites	3.5	4.5
9	73	F	Repair of bowel fistula	5.7	5.9
10	70	M	Strangulated inguinal hernia	3.2	6.8
11	23	M	Multiple fractures	1.7	3.1
12	58	M	Multiple fractures	2.0	4.0
13	47	M	Abdominal stab wound	1.8	2.3
14	25	M	Perforated appendix	1.7	2.8
15*	55	M	Small bowel obstruction	1.5	2.1
16	55	M	Emergency tracheotomy	1.4	1.5
17	65	M	Bleeding duodenal ulcer	4.9	5.9
18	19	M	Abdominal stab wound	2.0	5.1
19	21	M	Abdominal stab wound	2.0	2.8
20	20	M	Stab wound	5.9	6.5

The change in pH for each subject is shown in figure 1; the difference is statistically significant ($P < 0.001$). The number of patients with an aspirate pH less than 2.5 decreased with time after cimetidine (fig. 2). During surgery the pH increased to greater than 4 in all patients, and greater than 5 in all but one, and remained greater than 4 in all patients at the time of tracheal extubation.

No patient developed a pulmonary complication; there were no deaths or even side-effects which could be attributed to cimetidine.

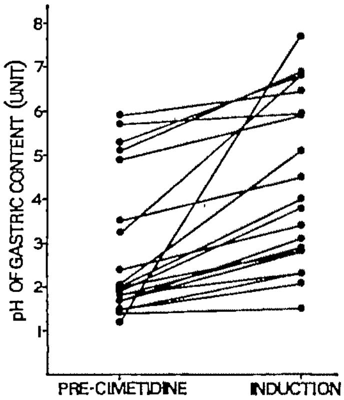

FIG. 1. Change in the pH of gastric contents in the 60 min between receiving cimetidine and induction of anaesthesia.

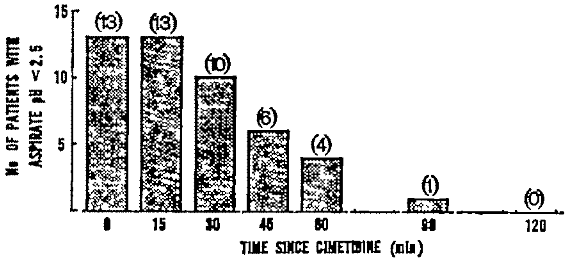

FIG. 2. Number of patients with a gastric aspirate pH of less than 2.5 at different times after cimetidine.

DISCUSSION

It is generally thought that the critical pH for pulmonary complications following aspiration of stomach contents is 2.5 (Roberts and Shirley, 1974; Editorial, 1977) although there has been a case report of pulmonary symptoms developing after aspiration of material with a greater pH (Taylor, 1975).

Oral antacids are used widely for increasing intragastric pH before emergency surgery and a number of studies have assessed the effectiveness of antacid therapy. These have shown 42–55% (Taylor and Pryse-Davies, 1966; Roberts and Shirley, 1974) of obstetric patients and 46–63% (Hester and Heath, 1977; Stoelting, 1978) of elective non-obstetric patients to have a gastric aspirate pH of less than 2.5 without treatment.

In the present study 13 patients (65%) had a pH of less than 2.5 before treatment and this decreased to four (20%) at induction of anaesthesia, 1 h after cimetidine had been given. In these four patients no common factor was found, such as diagnosis, volume of aspirate at induction, or time since last meal, to account for the failure to respond rapidly to cimetidine. In obstetric patients given magnesium trisilicate the proportion of patients with a pH remaining less than 2.5 has varied widely, being reported variously as none (Taylor and Pryse-Davies, 1966), 8.5% (Peskett, 1973), 16% (Roberts and Shirley, 1974) and 20% (White, Clarke and Stanley-Jones, 1976). Cimetidine therefore reduced the proportion of patients with a pH less than 2.5 to a number similar to that achieved by some investigators with oral antacids, even though a greater proportion of patients than is usual in obstetrics had an initial pH of less than 2.5. In elective non-obstetric patients Hutchinson and Newson (1975) found that the proportion with a gastric aspirate pH less than 2.5 was 53% in untreated controls and 19% in those receiving magnesium trisilicate 30 min or more before anaesthesia. However, magnesium trisilicate given less than 30 min before anaesthesia was considerably more effective.

An important disadvantage of cimetidine for use before emergency surgery is that no worthwhile effect was seen until 45 min after injection. However, the delays in organizing emergency surgery, such as documentation, completion of investigations, cross-matching of blood and preparation of the surgical instruments, are such that in none of the patients was anaesthesia induced before 1 h after the injection of cimetidine, and in practice the cimetidine had to be withheld until 1 h before the time arranged for surgery. The continued increase in pH observed after 1 h suggests that cimetidine given as soon as possible would be even more effective. This is supported by the results of Husemeyer, Davenport and Rajasekaran (1978) who found in elective gynaecological surgery that oral cimetidine 400 mg 2.5–9 h before induction of anaesthesia reduced, from 70% to 90%, the proportion of patients with a gastric aspirate pH of less than 2.5 after induction of anaesthesia. The prolonged action of cimetidine means that at the time of extubation and in the early recovery period, when patients are again at risk, the pH of gastric contents remains high.

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LA CIMETIDINE POUR LA PREVENTION DU SYNDROME DE MENDELSON—ASPIRATION D'ACIDE PULMONAIRE

RESUME

On a administré 200 mg de cimétidine par voie intraveineuse, 1 h avant l'induction de l'anesthésie, à 20 malades sur le point de subir une intervention chirurgicale d'urgence. Il y a eu une augmentation du pH de la déglutition gastrique chez tous les malades ($P<0{,}001$) et dans 80% des cas le pH a été supérieur à 2,5 unités au moment de l'induction de l'anesthésie. Le pH de la déglutition gastrique a continué à augmenter après l'induction de l'anesthésie et était supérieur à 4 unités chez tous les malades au moment de l'extubation trachéale et au début de la période de récupération.

CIMETIDIN ZUR VORBEUGUNG DES PULMONAREN SÄUREANSAUGUNGSSYNDROMS (MENDELSON)

ZUSAMMENFASSUNG

Cimetidin (200 mg) wurde 20 Patienten 1 Stunde vor Narkose für Notoperationen verabreicht. Es gab einen Anstieg von pH bei der gastrischen Ansaugung aller Patienten ($P<0{,}001$), und bei 80% war pH grösser als 2,5 Einheiten bei Narkosebeginn. Das pH der gastrischen Ansaugung stieg nach Narkosebeginn weiter und war bei allen Patienten grösser als 4 Einheiten zum Zeitpunkt der Entfernung des Trachealrohres und der ersten Erholungszeit.

CIMETIDINA EN PREVENCION DEL SINDROME (DE MENDELSON) DE ASPIRACION PULMONAR ACIDA

SUMARIO

Se administró a 20 pacientes a punto de someterse a operaciones de emergencia 200 mg de cimetidina i.v. 1 h antes de la inducción de la anestesia. Se observó un aumento del pH del aspirado gástrico de todos los pacientes ($P<0{,}001$) y en el 80% de ellos, el pH era mayor de 2,5 unidades al momento de la inducción de la anestesia. El pH del aspirado gástrico siguió aumentando después de la inducción de la anestesia y era mayor de 4 unidades en todos los pacientes al momento de la extubación traqueal y al principio del periodo de recuperación.

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A STUDY OF THE PLASMA CONCENTRATIONS OF LORAZEPAM IN MOTHER AND NEONATE

R. J. McBride, J. W. Dundee, J. Moore, W. Toner and P. J. Howard

SUMMARY

A standard dose of lorazepam 2.5 mg was given i.v. to two groups of mothers: (a) before surgical induction of labour and (b) at the beginning of the second stage of labour. A group of non-pregnant women was studied as control. Plasma concentrations of lorazepam were measured by gas–liquid chromatography, in the mothers before delivery, and in the mother and neonate at delivery and 24 and 48 h thereafter. Concentrations at delivery in the neonates were similar to those in the mothers in group (a), but significantly less in group (b). Fetal concentration rarely exceeded that in the mother. Measurements after delivery indicated that the neonates were able to metabolize lorazepam at the same rate as the mothers. Of the 22 neonates studied only one had an Apgar score of less than 8 at 5 min and this score was 10 at 10 min.

The use of parenteral analgesia during labour is a common and widespread practice, but it is well known that the pain and discomfort of labour has not only a physical component but also an emotional one. The fear of experiencing physical pain may cause considerable anxiety before and during the early stages of labour. The introduction of the benzodiazepine drugs with their soporific and anxiolytic properties led to the use of diazepam in conjunction with the more traditional analgesics. The aim was to abolish the mother's fear and anxiety about the pain of labour. An early study (Bepko, Lowe and Waxman, 1965) showed that parenteral diazepam markedly reduced apprehension and discomfort associated with labour and also the amount of parenteral analgesic required. Later studies by Flowers, Rudolph and Desmond (1969) and Niswander (1969) supported these findings. However, the babies of some of the mothers who received diazepam showed temporary hypoactivity and hypotonia. Other reports have confirmed these observations, especially if large doses of diazepam were given (Owen, Irani and Blair, 1972; McCarthy, O'Donnell and Robinson, 1973).

Lorazepam is the o-chlorophenyl derivative of the main metabolite of diazepam and has been found to be useful as an oral, i.m. or i.v. premedicant (Dundee et al., 1977). It has good soporific, anxiolytic and amnesic properties. We have examined its use in obstetric practice.

PATIENTS AND METHODS

Three groups of patients were studied: a control group of 10 non-pregnant patients undergoing routine minor gynaecological procedures (premedicant group); 10 pregnant women undergoing surgical induction of labour, to whom the drug was given before the procedure (first stage group); 12 parturients to whom the drug was given at the beginning of the second stage of labour (second stage group). All the pregnant mothers had an uncomplicated ante-natal history and were expected to undergo spontaneous vaginal delivery.

None of the patients was receiving any medication containing a benzodiazepine. Informed consent was obtained from each patient on the day before operation or labour except for a number of patients in the second stage group who gave consent during the first stage of labour, following admission to the labour ward. Patients in the first and second stage groups were comparable with respect to weight and height, as were the premedicant group, except that, as expected, the weights of this last group were less (table I).

A standard dose of lorazepam 2.5 mg was given i.v. over a period of 15 s into a large forearm vein. This was considered to be near to the optimum dose to produce adequate sedation in adults.

Venous blood was sampled (5–10 ml) via a cannula and three-way tap from the contralateral forearm

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TABLE I. *Mean (± SEM) age, weight and height of the three groups of patients in the study*

Group	n	Age (yr)	Weight (kg)	Height (cm)
Premedicant	10	27.8 ± 3.10	53.4 ± 3.12	159.2 ± 2.43
First stage	10	29.2 ± 2.48	72.4 ± 2.32	156.0 ± 1.53
Second stage	12	27.5 ± 1.25	69.8 ± 2.07	161.2 ± 1.62

and placed in heparinized tubes. Samples of about 1 μl were obtained from the neonates by heel prick. Sampling times are in table II. All samples were centrifuged within 2 h of collection and stored at −20 °C in non-heparinized tubes to await analysis.

TABLE II. *Sampling scheme*

Group	Sampling times
Premedicant	Before injection, 2, 5, 10, 15, 30, 60, 90, 120 min and hourly until 480 min after injection and at 24 h after injection.
First stage	Before injection, 2, 5, 10, 15, 30, 60, 90, 120 min and hourly until delivery. At delivery sample from mother and mixed cord blood sample. At 24 and 48 h after delivery, sample from the mother and a micro sample from the neonate.
Second stage	Before injection, 2, 5, 10, 15, 30, 60, 90, 120 min after injection. At delivery sample from mother and mixed cord blood sample. At 24 and 48 h after delivery, sample from mother and micro sample from neonate.

Analysis was performed by gas–liquid chromatography following benzene extraction as described by Howard and others (1977) and modified by Howard and others (1978) for micro samples. All the samples for a particular patient and her baby were analysed on the same day by one operator using the same standard and column.

The condition of the infant was assessed at 1 and 5 min after delivery using the 10-point Apgar score.

RESULTS

The mean plasma concentrations of lorazepam are shown in figure 1. The drug "decay profiles" are similar in the three groups. The only significant variation was between the premedicant and the first stage groups at 120 min after injection, where there was a difference between the means ($P < 0.05$).

The injection–delivery times in the first stage group ranged from 180 to 447 min (mean 293). The neonatal mean plasma lorazepam concentration at delivery was not significantly different from that of the mothers ($P > 0.1$) (table III; fig. 2). In the second stage group the injection–delivery time range was 5–67 min (mean 21) with nine of the 12 being within 20 min). In this group the neonatal mean plasma lorazepam concentration was significantly smaller ($P < 0.005$) than that of the mothers (fig. 3).

Figure 4 shows the ratio of neonatal to maternal plasma lorazepam concentration at delivery. In the first stage group this value was in the range 0.85–1.33 ng ml^{-1} (mean 1.04 ± 0.05), whereas in the second stage group the range was 0.59–1.21 ng ml^{-1} (mean 0.76 ± 0.05). Only when delivery occurred more than 240 min after injection was the neonatal–maternal ratio greater than unity.

The ability of the neonate to redistribute and metabolize the drug is of vital importance and the results show that the neonates of both groups were able to remove lorazepam from the plasma at the same rate as the mothers (figs 5, 6). The mean plasma lorazepam concentrations at 24 and 48 h in the infants of the first stage group were 17.6 ± 1.30 and 13.4 ± 1.83 ng ml^{-1} respectively, with the corresponding maternal means 17.0 ± 1.79 and 12.5 ± 1.83 ng ml^{-1}. The mean concentrations at 24 and 48 h in the infants of the second stage group were 13.25 ± 1.20 and 10.30 ± 1.30 ng ml^{-1} respectively and corresponding maternal concentrations at the same time intervals were 12.40 ± 0.80 and 7.80 ± 1.20 ng ml^{-1}.

The decrease in plasma lorazepam concentration in both mother and neonate in each group between the time of delivery and 24 h after delivery was highly significant ($P < 0.001$). The plasma lorazepam values at 24 and 48 h after delivery were very small and approached the lower limit of sensitivity of the method of detection.

The Apgar scores of the neonates and the plasma lorazepam concentrations at delivery are shown in table IV. All the scores were good except in two patients in the first stage group who appeared to have abnormalities of the fetal heart rate during second stage (Type II dips). One of these mothers had received pethidine 100 mg i.m. 22 min before delivery.

DISCUSSION

The pattern of plasma lorazepam concentrations in all three adult groups in this study was similar to those published by Elliott (1976) and Dundee and others (1978), although our absolute values were smaller because of the dose used. Thus it would

TABLE III. *Maternal and infant plasma lorazepam concentrations (ng ml $^{-1}$) at delivery in individual patients following i.v. administration of lorazepam 2.5 mg to mother. ID (min) = time from injection to delivery*

First stage group												
ID (min)	192	330	404	200	257	305	180	259	354	477		
Mother	35	25	26	34	39	22	33	23	21	21		
Infant	30	26	30	29	37	23	36	23	28	25		
Second stage group												
ID (min)	8	19	67	60	5	7	10	35	10	12	12	10
Mother	64	49	50	50	70	78	68	52	61	73	67	77
Infant	51	39	32	45	82	65	51	38	37	43	46	46

appear that the parturient was able to metabolize and excrete lorazepam at the same overall rate as a non-pregnant patient. The significant difference between the mean plasma concentrations of the premedicant group and the first stage group at 120 min may be attributed to the distribution of a standard dose of lorazepam throughout the significantly greater body mass of the pregnant patient (table I). The neonatal (mixed cord) plasma concentrations were small in the second stage group even though the maternal plasma concentrations were large, but the injection–delivery time was short. In the other group, despite delivery several hours after administration of i.v. lorazepam, the neonatal plasma concentrations were not greater than those of the mothers; by this time the plasma concentrations in the mother were small.

There is no published comparison of plasma lorazepam concentrations with soporific action. However, Dundee and others (1979) found no drowsiness 24 h after premedication, with plasma concentrations of 21–50 ng ml^{-1}. We conclude that concentrations of 30–40 ng ml^{-1} found at delivery in this study did not have a soporific action, although the anxiolytic action was still evident.

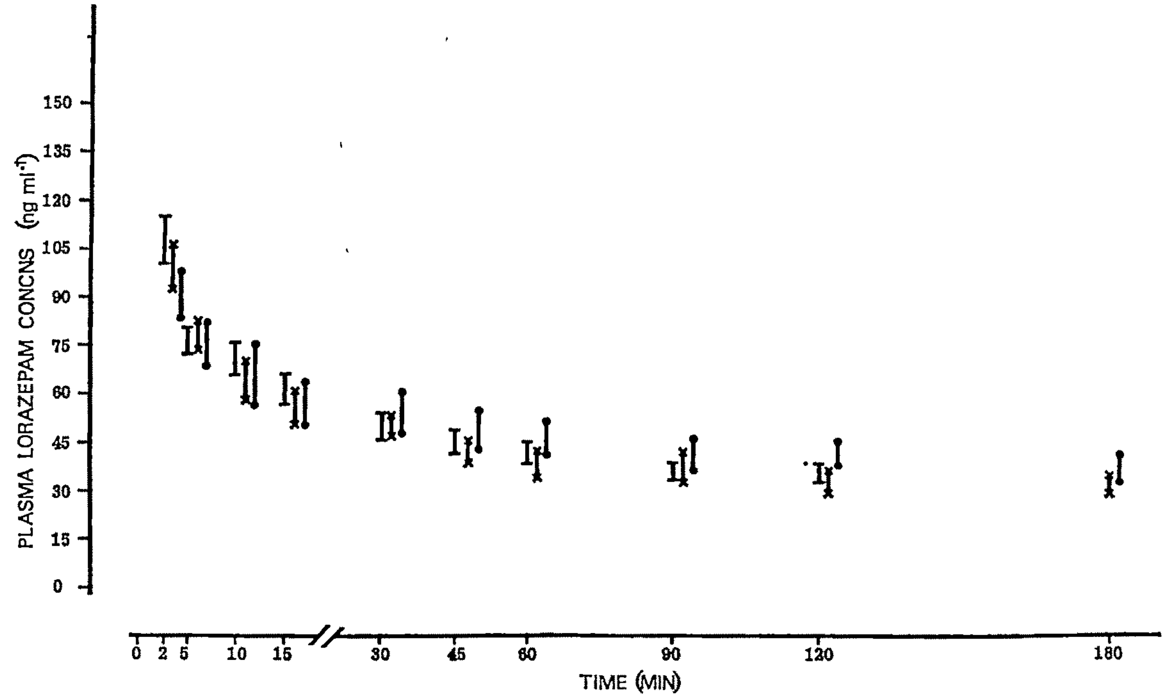

FIG. 1. Mean ± SEM plasma lorazepam concentrations of the three groups following i.v. administration of lorazepam 2.5 mg: — = second stage; × = first stage; ● = premedicant group.

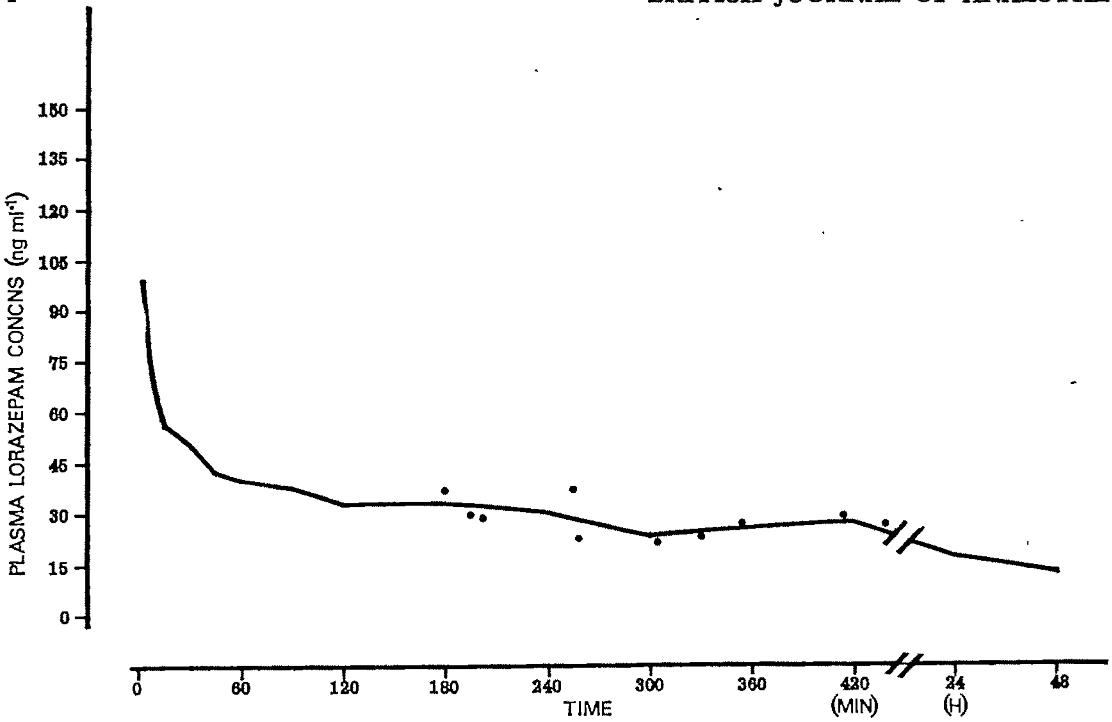

FIG. 2. Mean plasma lorazepam concentrations of the mothers in first stage group with the plasma concentrations of the individual neonate shown at the time of delivery (●).

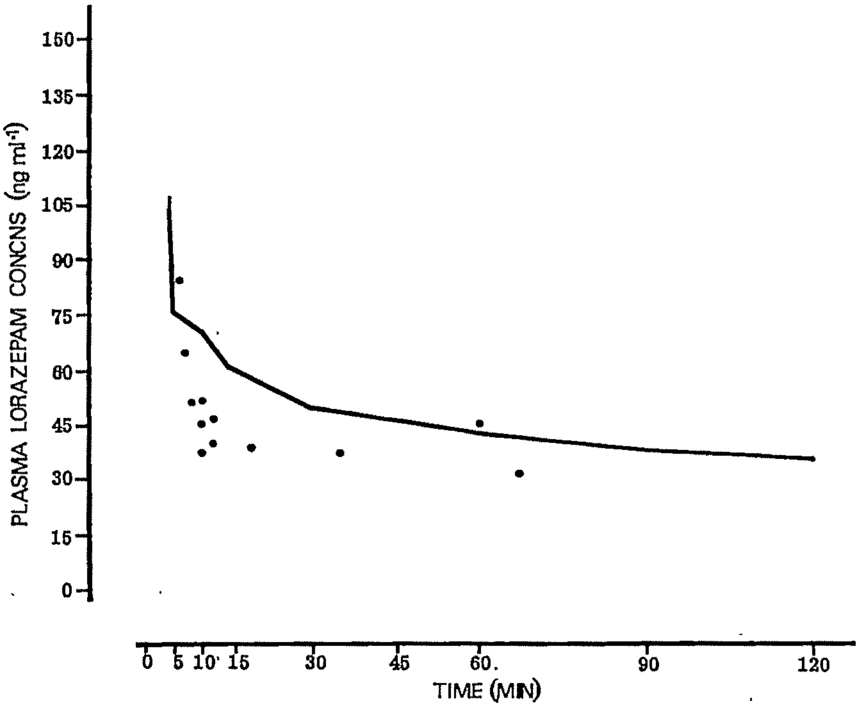

FIG. 3. Mean plasma lorazepam concentrations of the mothers of the second stage group with the plasma concentrations of the individual neonate shown at the time of delivery (●).

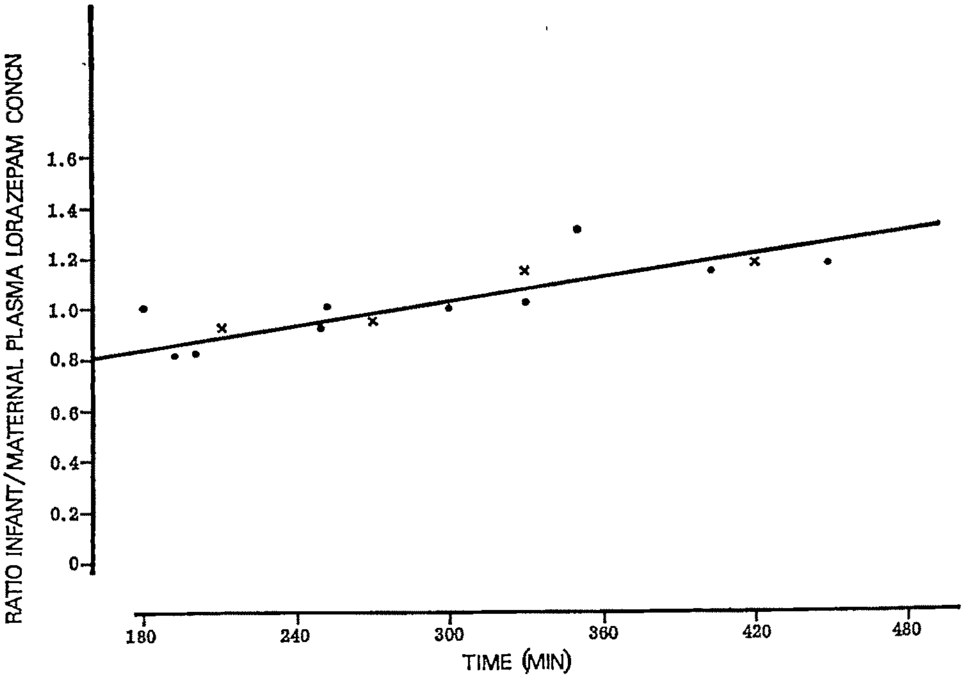

FIG. 4. Neonatal–maternal lorazepam concentration ratio at delivery for each neonate in the first and second stage groups (× = mean ratios at time intervals 121–200, 201–280, 281–360 and more than 360 min).

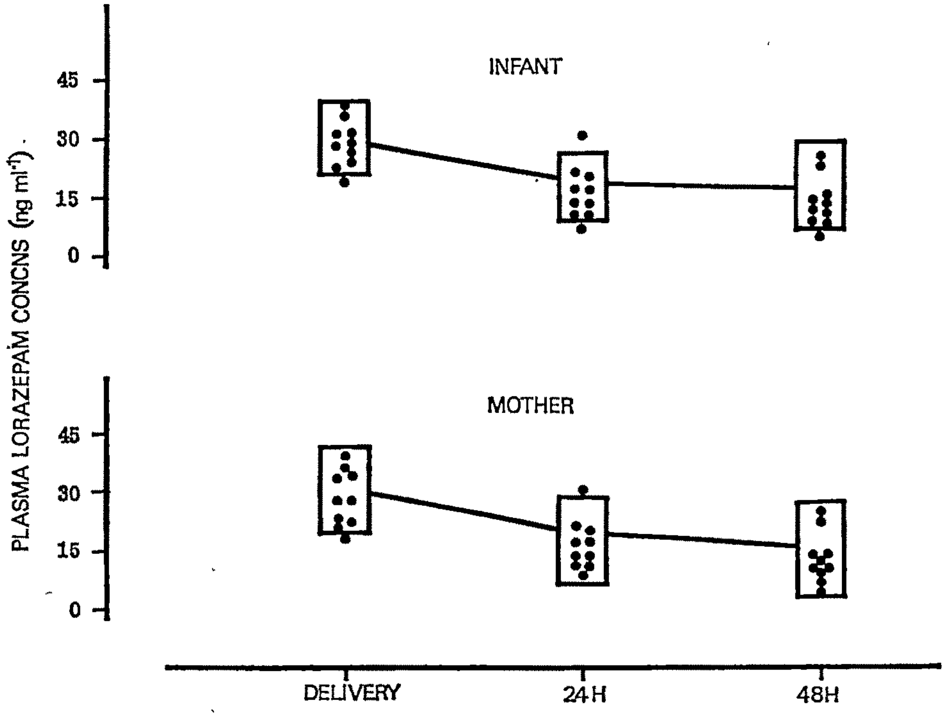

FIG. 5. Scatter of individual plasma lorazepam concentrations of first stage group neonates and mothers at delivery, 24 and 48 h after delivery. The range of the boxes is mean ± 2 SD.

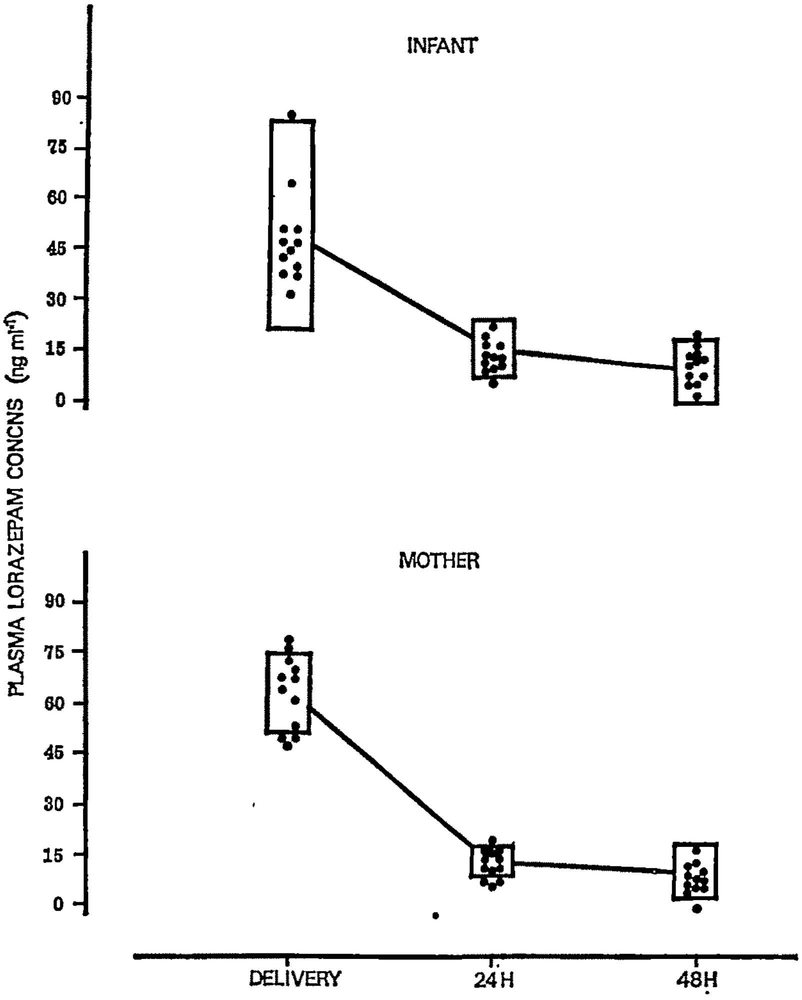

FIG. 6. Scatter of individual plasma lorazepam concentrations of second stage group neonates and mothers at delivery, 24 and 48 h after delivery. The range of the boxes is mean ± 2 SD.

The findings relating to the neonate at delivery are different from those produced by diazepam. Gamble and others (1977) found significantly greater diazepam concentrations in the neonates than in the mothers at delivery. Lorazepam does not appear to cross the placental barrier as readily as diazepam. Our plasma lorazepam neonate–maternal ratio was 0.59–1.21 (mean 0.76 ± 0.05) for the second stage group and 0.85–1.33 (mean 1.05 ± 0.05) for the first stage group. Gamble and others (1977) reported a range for diazepam of about 0.8–2.6, with a noted increase if the diazepam injection–delivery time was more than 1 h.

The ability of a drug to cross cell membranes is influenced by degree of ionization, lipid solubility, molecular weight and concentration gradient. Lorazepam has a molecular weight (321.2) similar to that of diazepam (284.7). It has two pKa values—at 1.3 and 11.5 (Smith and Rawlins, 1973)—and therefore at blood pH it is largely in the un-ionized form. Little is known about the protein binding of lorazepam in the fetus or neonate, but it is thought that only between 70 and 80% is protein-bound in the adult. However, it is obvious from our results that lorazepam does not cross the placenta rapidly and does not appear in great concentrations in plasma in the neonate.

TABLE IV. *Relationship between neonatal plasma lorazepam concentration at delivery and Apgar score. *Fetal heart monitor showed Type II dips during second stage: forceps delivery, baby given sodium bicarbonate and 50% dextrose i.v. at delivery, cried well and thrived. **Mother given pethidine 100 mg i.m. 22 min before delivery: fetal heart monitor showed Type II dips during second stage, baby given naloxone 7 min after delivery, Apgar score 10 at 10 min*

Group	Neonatal plasma lorazepam (ng ml^{-1})	Apgar score of infant	
		1 min	5 min
First stage	30	9	10
	26	4	8*
	30	9	10
	29	7	9
	37	1	5**
	23	9	10
	36	8	10
	23	8	10
	28	8	10
	25	7	9
Second stage	51	8	10
	39	7	10
	50	8	10
	45	8	10
	85	7	10
	65	7	9
	51	9	10
	38	6	8
	37	8	10
	43	8	10
	46	8	10
	46	9	10

The neonate's lorazepam "load" at delivery was dealt with (metabolized or excreted) as rapidly as the mother's in both first and second stage groups (figs 5, 6). Plasma concentrations in the neonate 24 h after delivery were similar to those of the respective mother. Metabolism of lorazepam is a one-stage process involving the production of a glucuronide, which itself has no pharmacological activity and is excreted easily. However, it is possible that metabolism might be retarded in the premature neonate with reduced enzymatic function in the liver. This result is different from that reported for diazepam; there remains a much greater plasma concentration of diazepam in the neonate 24 h after delivery (Gamble et al., 1977). Diazepam is metabolized relatively easily by the neonate, but one of its metabolites, n-desmethyldiazepam, is pharmacologically active for a considerable time.

All the neonates studied thrived during their time in hospital and none was retained longer than normal for the degree of parity of the mother, except when breast feeding was being established. The two low Apgar scores in the first stage group could be attributed to obstetric complications and, in one case, to the administration of an analgesic near the time of delivery.

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ETUDE SUR LES CONCENTRATIONS DE LORAZEPAM DANS LE PLASMA CHEZ LA MERE ET LE NOUVEAU-NE

RESUME

On a administré par voie intraveineuse une dose standard (2,5 mg) de lorazépam à deux groupes de mères: (a) avant l'induction chirurgicale du travail et (b) au commencement du second stade du travail. Un groupe de femmes qui n'étaient pas enceintes a servi de groupe témoin. Les concentrations de lorazépam dans le plasma ont été mesurées par la chromatographie en phase gazeuse–liquide chez les mères, avant l'accouchement et chez les mères et les nouveaux-nés au moment de l'accouchement de même que 24 h et 48 h plus tard. Les concentrations chez les nouveaux-nés, au moment de leur naissance, étaient similaires à celles de leurs mères dans le groupe (a), mais nettement moindres dans le groupe (b). Les concentrations foetales ont rarement été supérieures à celles des mères. Les mesures prises après l'accouchement indiquent que les nouveaux-nés ont été à même de métaboliser le lorazépam au même rythme que les mères. Sur les 22 nouveaux-nés que l'on a études un seul avait un indice d'Apgar inférieur à 8 à 5 min et, dans l'ensemble, leur indice a été de 10 à 10 min.

EINE STUDIE DER PLASMAKONZENTRATIONEN VON LORAZEPAM BEI MUTTER UND NEUGEBORENEM

ZUSAMMENFASSUNG

Eine Standarddosis von 2,5 mg Lorazepam wurde intravenös an zwei Gruppen von Müttern verabreicht: (a) vor chirurgischer Weheneinleitung, (b) bei Beginn der 2. Stufe der Wehen. Eine Gruppe nicht-schwangerer Frauen wurde als Kontrollgruppe studiert. Die Lorazepam-Plasmakonzentrationen wurden durch Gas-Flüssigkeitschromatographie gemessen—in den Müttern vor der Geburt, und in Mutter und Kind bei der Geburt, sowie 24 und 48 Stunden danach. Konzentrationen bei der Geburt waren in den Neugeborenen ähnlich wie bei den Müttern in Gruppe (a), aber wesentlich geringer als in Gruppe (b). Die foetale Konzentration überstieg selten die bei der Mutter. Messungen nach der Geburt lassen erkennen, dass die Neugeborenen Lorazepam in derselben Zeit umsetzen können wie die Mütter. Von den 22 untersuchten Neugeborenen wies nur eines Apgarwerte von unter 8 bei 5 min auf, und ihre Werte betrugen 10 bei 10 min.

UN ESTUDIO DE CONCENTRACIONES PLASMATICAS DE LORAZEPAM EN MADRES Y NEONATOS

SUMARIO

Se administró una dosis standard de 2,5 mg de lorazepam a dos grupos de madres: (a) antes de la inducción quirúrgica del parto y (b) al principio de la segunda fase del parto. Se realizó el estudio de un grupo de mujeres no-embarazadas, como control. Se midieron por cromatografía gas-líquido las concentraciones de lorazepam en el plasma de las madres antes del parto y en madres y neonatos al momento del parto y 24 y 48 h después. Al momento del parto, las concentraciones en los neonatos eran similares a las de las madres del grupo (a), pero mucho más bajas en el grupo (b). Las concentraciones en los fetos raramente excedían de las de las madres. Las mediciones después del parto demostraron que les neonatos podían metabolizar el lorazepam con la misma rapidez que sus madres. De los 22 neonatos estudiados, uno solo tenía un recuento de menos de 8 a 5 min, y de 10 a 10 min.

Br. J. Anaesth. (1979), **51**, 979

BREATH-BY-BREATH HALOTHANE MONITORING DURING ANAESTHESIA

A study in children

P. MORRIS, M. L. TATNALL AND P. G. WEST

SUMMARY

The use of a halothane meter in routine paediatric anaesthesia with controlled ventilation is described. The results demonstrate the accuracy achieved in the control of the alveolar halothane concentration. Measurement of the alveolar halothane concentration revealed responses to surgical stimulation otherwise obscured by neuromuscular blockade, and this may indicate insufficient depth of anaesthesia.

Volatile anaesthetic agents are administered on the basis of clinical observation and pharmacological knowledge. Calibrated vaporizers provide more predictable inspired concentrations, but measurement of the expired concentration is required to provide information on the rate of uptake and alveolar concentration of the drug.

Routine measurement of the alveolar anaesthetic concentration would enable the extensive data on MAC values (Eger, 1974) to be applied, resulting in more precise control of anaesthesia. We present examples of results obtained using a rapid response meter to measure the inspired and alveolar concentrations of halothane and discuss the value of continuous breath-by-breath monitoring in clinical anaesthesia.

PATIENTS AND METHODS

Fifty fit, healthy children aged 6 months to 13 yr (weight 9–35 kg) were studied during anaesthesia for routine abdominal, urological or orthopaedic surgery. Premedication comprised either oral trimeprazine tartrate 3 mg kg^{-1} 2½ h before operation or papaveretum 0.4 mg kg^{-1} and hyoscine 0.06 mg kg^{-1} i.m. 1 h before operation. An i.v. infusion was established and anaesthesia was induced with thiopentone 6 mg kg^{-1} followed by pancuronium 0.1 mg kg^{-1}. The trachea was intubated with a snug fitting Portex uncuffed oral endotracheal tube and controlled ventilation of the lungs commenced with either 100% oxygen or 70% nitrous oxide in oxygen using a Blease Pulmoflater with a paediatric attachment. The minute volume required to maintain Pa_{CO_2} 5.3 kPa (40 mm Hg) at a respiratory rate of 14–18 b.p.m. was calculated (Nunn, 1977). Halothane was added from a Fluotec Mark 3 vaporizer either at a constant inspired concentration or by the use of "overpressure" (an initially high concentration which was reduced subsequently). Heart rate, e.c.g. and temperature were monitored continuously. The systolic arterial pressure was recorded regularly by indirect sphygmomanometry.

The halothane meter (Tatnall, West and Morris, 1978) was situated in the expiratory limb of the ventilator circuit close to the endotracheal tube connector (fig. 1).

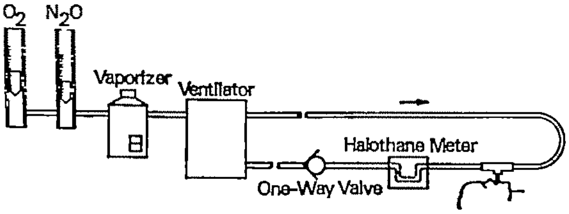

FIG. 1. Schematic diagram of the anaesthetic breathing system showing the position of the halothane meter.

The inspired concentration was quantified by measurement of the concentration in the initial fraction of expired gas (deadspace gas). No ventilation/perfusion inequality was detected in any patient and the end-tidal concentration was assumed to represent the alveolar concentration (Eger and Bahlman, 1971). Utilizing the MAC value for halothane (Saidman et al., 1967) an equilibrium

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alveolar concentration was calculated for each patient.

Towards the end of surgery the halothane was discontinued and the rate of decrease of alveolar concentration observed. On completion of surgery the residual neuromuscular blockade was antagonized with neostigmine 0.07 mg kg^{-1} and atropine 0.02 mg kg^{-1} i.v. Ventilation was continued with 100% oxygen and the tracheal tube removed when spontaneous respiration had been re-established.

RESULTS

The relatively slow increase in alveolar concentration towards equilibrium in response to a constant inspired concentration is illustrated in figure 2. The concentration achieved finally was substantially smaller than that inspired. If insufficient time was allowed before surgery commenced or if the selected inspired concentration was too small during maintenance, a decrease in the alveolar concentration from that expected was observed following surgical stimulation.

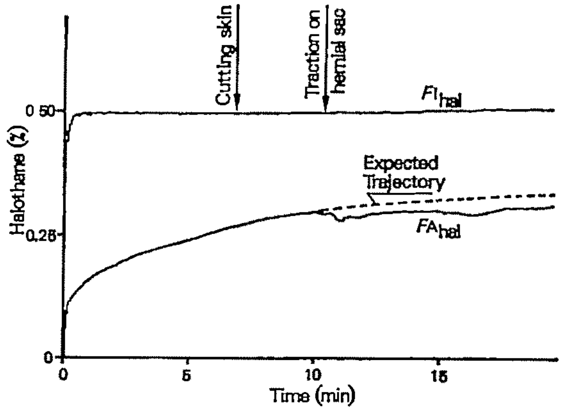

FIG. 2. Decrease in alveolar halothane concentration in response to surgical stimulation. Patient: 7 yr, 25 kg. Operation: inguinal herniotomy. Minute volume: 3.8 litre min^{-1}; nitrous oxide and halothane.

Such a response (fig. 2) occurred in four of 10 patients anaesthetized to a cumulative MAC value of 1.0 × MAC. No signs of inadequate anaesthesia, including movement, were detected in these patients. In 40 patients in whom a cumulative MAC value of 1.2 × MAC was used, this response was not observed. Figure 3 illustrates the use of "overpressure" to attain rapidly and maintain a constant alveolar concentration of 1% halothane.

Figure 4 illustrates the precise control of the alveolar concentration which was possible by applying

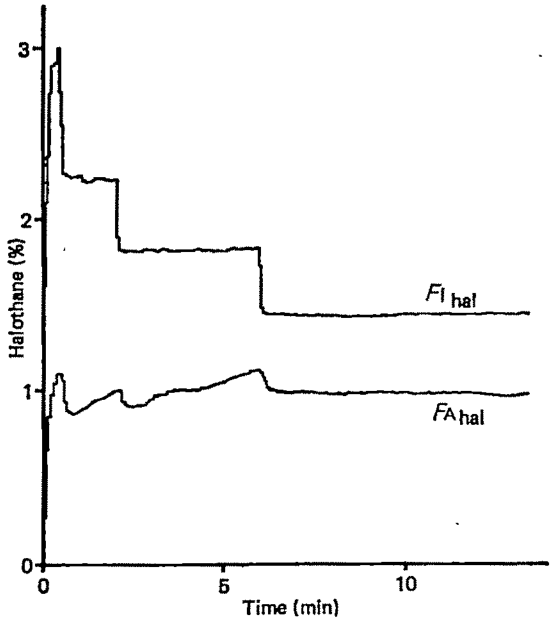

FIG. 3. Inspired concentration "overpressure" using large decremental steps to attain a constant alveolar concentration of 1.0% halothane. Patient: 5 yr, 26 kg. Operation: soft tissue release right foot. Minute volume: 3.8 litre min^{-1}; oxygen and halothane.

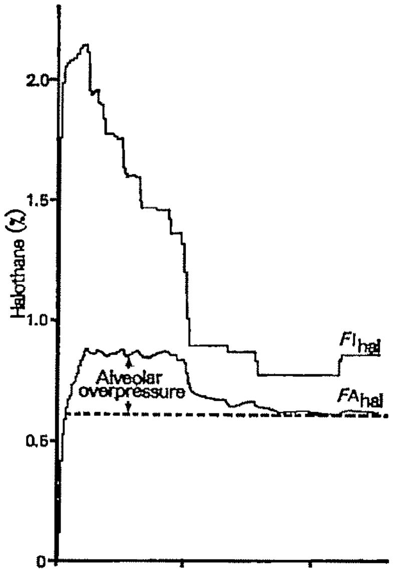

FIG. 4. Application of alveolar concentration "overpressure". Patient: 11 yr, 28 kg. Operation: inguinal herniotomy. Minute volume: 4.0 litre min^{-1}; nitrous oxide and halothane.

small decremental adjustments in the inspired concentration. In this patient a greater alveolar concentration was sustained initially before reduction to that required for maintenance; this technique could be described as "alveolar overpressure".

Figure 5 demonstrates the different rates of decrease in avelolar concentration when halothane was discontinued in three patients (of comparable weight) in whom anaesthesia had been maintained at a constant alveolar concentration of 0.6% for 12.5, 30.5 and 610 min respectively. The time taken for the alveolar concentration to decrease by 75% was 2.5, 6.5 and 19.5 min respectively.

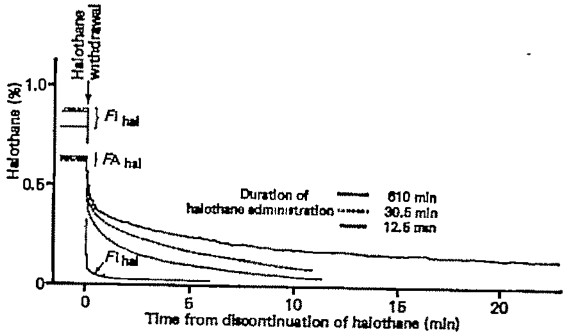

FIG. 5. The influence of the duration of anaesthesia upon the rate of decrease of avelolar halothane concentration following withdrawal. Patient: 13 yr, 33 kg; operation: removal of pelvic tumour; MV: 4.2 litre min^{-1}, N_2O+hal; duration: 610 min. Patient: 11 yr, 30 kg; operation: orchidopexy; MV: 4.1 litre min^{-1}, N_2O+hal; duration: 30.5 min. Patient: 11 yr, 28 kg; operation: inguinal herniotomy; MV: 4.0 litre min^{-1}, N_2O+hal; duration: 12.5 min.

DISCUSSION

Using a constant vaporizer setting many factors including variation in vaporizer output (Adams, 1977), the constituent materials, capacity and type of anaesthetic breathing system (Eger, Larson and Severinghaus, 1962), the second gas effect (Epstein et al., 1964) and patient variability, influence both the inspired concentration and the trajectory of the alveolar concentration curve.

The problem of estimating the complex dynamic relationship between vaporizer setting and alveolar concentration is eliminated by the use of breath-by-breath measurement and this enables the safe use of "overpressure" to attain the required alveolar concentration. The time constants involved in the relationship between the alveolar and brain halothane concentrations (Mapleson, 1973) may be used as a guide in the use of "alveolar overpressure"(the logical extension of inspired "overpressure") to accelerate the transition to the required brain concentration during induction of anaesthesia.

The concept of MAC provides the anaesthetist with definable objectives regarding the alveolar concentration appropriate for satisfactory anaesthesia in 50% of patients. Recently an expanded MAC, calculated to encompass 95% of patients, has been reported (de-Jong and Eger, 1975), thus extending the usefulness of this index. For example, MAC for halothane in adults is 0.74% whilst the expanded MAC_{95} is 0.90% or 1.2×MAC. Thus, by taking into account the variation of MAC with age (Gregory, Eger and Munson, 1969) and the MAC fractions of all the components of the anaesthetic sequence (Saidman and Eger, 1964), the equilibrium alveolar halothane concentration required to anaesthetize 95% of all patients may be determined.

The reduction in alveolar concentration associated with surgical stimulation during induction and maintenance of anaesthesia may be explained by an increase in cardiac output since ventilation was controlled and factors which would significantly alter the mixed venous anaesthetic concentration (for example a blood transfusion) were not applicable. Stimulation of the peritoneum was more likely to produce this response than was cutting the skin, the standard for MAC evaluation in man.

It has been suggested that the cardiovascular responses from autonomic activity during surgery may be considered as part of a general stress syndrome (Savege, DuBois and Holly, 1978). The results obtained from four of the patients anaesthetized to 1.0×MAC may be interpreted as indicating insufficient depth of anaesthesia.

Following withdrawal of inhalation agents, the rate of decrease of alveolar concentration has been used to define recovery (Stoelting and Eger, 1969), and the patient's ability to respond to verbal commands and maintain his own airway is related to the alveolar concentration (Stoelting, Longnecker and Eger, 1970). Continuous observation of the alveolar halothane concentration during this stage of anaesthesia enables the anaesthetist to recognize the time at which recovery can be expected to occur and is of particular value following long anaesthetics where increased body saturation has occurred.

Measurement of depth of anaesthesia is vague and correlates poorly with clinical signs (Cullen et al., 1972), especially if neuromuscular blocking agents have been administered, thus denying information available from respiratory parameters and movement in response to surgery. Routine measurement of the arterial blood anaesthetic concentration is impractical, but when using inhalation agents instantaneous measurement of the alveolar concentration may be readily performed. This has the advantage of being non-invasive and causes minimal interference with surgery.

It is clear that breath-by-breath monitoring is useful for other techniques of anaesthesia, including spontaneous ventilation and the use of the closed circuit. These applications are the subject of further study.

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SURVEILLANCE DE L'HALOTHANE SOUFFLE PAR SOUFFLE PENDANT L'ANESTHESIE

Etude effectuée sur des enfants

RESUME

L'usage d'un doseur d'halothane pour les anesthésies pédiatriques routinières avec ventilation contrôlée est décrit dans cet article. Les résultats obtenus démontrent que l'on a pu arriver à une bonne précision dans le contrôle de la concentration alvéolaire d'halothane. Les mesures de la concentration alvéolaire d'halothane ont révélé des réactions à la stimulation chirurgicale qui étaient jusqu'ici cachées par le blocage neuromusculaire, ce qui peut indiquer une insuffisance de la profondeur de l'anesthésie.

HALOTHANÜBERWACHUNG DES ATEMS WÄHREND DER NARKOSE: EINE STUDIE BEI KINDERN

ZUSAMMENFASSUNG

Die Verwendung eines Halothanmessers bei Routinenarkosen mit geregelter Belüftung bei Kindern wird beschrieben. Die Resultate zeigen die Genauigkeit, die bei der Kontrolle der alveolären Halothankonzentration erzielt wurde, deren Messung Reaktionen auf chirurgische Stimulierung enthüllte, die sonst durch neuromuskulare Blockierung verborgen bleiben. Dies könnte auch die unzureichende Stärke einer Narkose anzeigen.

CONTROL ALIENTO POR ALIENTO DEL HALOTANO DURANTE LA ANESTESIA

Un estudio en los niños

SUMARIO

Se describe el uso de un medidor de halotano en anestesia pediátrica ritinaria con ventilación controlada. Los resultados demuestran la exactitud lograda en el control de la concentración alveolar de halotano. La medición de la concentración alveolar de halotano reveló respuestas a la estimulación quirúrgica que, de otra manera, hubieran estado oscurecidas por el bloqueo neuromuscular, lo que puede indicar una intensidad insuficiente de la anestesia.

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KETAMINE AND AGENESIS OF THE CORPUS CALLOSUM

I. F. RUSSELL

SUMMARY

Ketamine did not provide adequate anaesthesia for pneumoencephalography in a 10-week-old child with agenesis of the corpus callosum. Associated neurological defects are the most likely reason for this failure.

Agenesis of the corpus callosum is a rare condition which may not be associated with any detectable neurological deficit. When a deficit does occur it is frequently related to the severity of associated brain anomalies (Harcourt-Webster and Rack, 1965). When agenesis of the corpus callosum is suspected in infancy pneumoencephalography is recommended for definitive diagnosis and general anaesthesia is usually required. The anaesthetic technique used for this procedure is rarely mentioned in published case reports. This communication describes the use of ketamine for pneumoencephalography in a 10-week-old child with suspected agenesis of the corpus callosum.

CASE REPORT

The baby was born with the aid of forceps at 36 weeks gestation and weighed 2600 g. He was the sixth child in an apparently normal family. Initial progress was uneventful until, at 5 weeks, he was admitted to hospital for investigation of vomiting; an abnormal increase in head size was noted. A ventriculogram suggested agenesis of the corpus callosum with hydrocephalus and a prosencephalic cyst of the right cerebral hemisphere. Pneumoencephalography under general anaesthesia was performed at the age of 10 weeks (weight 3990 g).

Premedication was with atropine 0.1 mg i.m. During the procedure, heart rate and ventilation were monitored with a precordial stethoscope and arterial pressure was measured with an infant pressure cuff and anaeroid manometer. Within 2 min of the injection of ketamine 50 mg i.m. (10.3 mg kg^{-1}) the muscles became rigid and the child exhibited extended limbs and opisthotonos. Arterial pressure, pulse and skin colour remained normal, but breathing became irregular. The rigidity decreased over the next few minutes and regular breathing was resumed. The baby was strapped into a modified infant seat and positioned for lumbar puncture. Over the next 30 min, while air was being injected for pneumoencephalography, a further 35 mg of ketamine (5-mg increments) was administered i.v. because of continued withdrawal movements in response to the insertion and positioning of the lumbar puncture needle. Because of persisting muscle stiffness, diazepam 0.5 mg was given i.v. over 3 min in an attempt to smooth the progress of the anaesthetic. Some muscle relaxation resulted, but the major effect was depression of breathing—a slowing of rate with deep jerky inspiratory efforts. Normal respiratory rhythm resumed within 10 min. Over the last hour of the procedure while x-rays were being obtained, a further 15 mg of ketamine was required (5-mg increments) and, during this time, the baby opened his eyes twice.

The investigation lasted 1 h 45 min and, except for respiratory rhythm, other signs were normal. Despite the large dose of ketamine (50 mg i.m. and 50 mg i.v.) the baby's eyes were open before leaving for the recovery area and there were no complications after anaesthesia. Ten days later, a repeat ventriculogram showed a significant increase in the size of the ventricles. A ventriculo-peritoneal shunt was performed under general anaesthesia with nitrous oxide, oxygen, halothane, tubocurarine and controlled ventilation; there were no problems during or after operation.

DISCUSSION

Ketamine is usually described as a "dissociative anaesthetic" because it produces e.e.g. changes suggesting dissociation of the cortex from the limbic system (Corssen, Miyasaka and Domino, 1968). However, more recent evidence does not entirely

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support this concept (Kayama and Iwama, 1972; Morse and Cave-Smith, 1974). Since Morse and Cave-Smith had successfully used ketamine to anaesthetize an infant with no cerebral cortex, it was decided to use ketamine on this occasion.

Although the procedure was performed successfully by an experienced radiologist, the anaesthetic was not ideal. Bizarre and uncontrolled neuromuscular activity in infants less than 6 months of age have been described with ketamine (Corssen, Miyasaka and Domino, 1968; Dillon, 1971; Szappanyos, Gemperle and Rifat, 1971). On the other hand, similar neuromuscular reactions have been observed in patients with pre-existing neurological deficiencies (Drury and Clark, 1970; Dillon, 1971). In this baby, opisthotonos and muscular stiffness could be described as a bizarre and uncontrolled reaction which did not respond to diazepam or to further increments of ketamine, a finding in agreement with the results of other work on normal infants (Szappanyos, Gemperle and Rifat, 1971). Conversely, the withdrawal movements initiated by stimulation from the lumbar puncture needle were well co-ordinated and suggested failure to achieve adequate analgesia. The reasons for the failure of ketamine are not clear.

While ketamine is usually described as a mild respiratory stimulant, large doses may cause depression of breathing. In this case respiratory depression occurred only following the administration of diazepam. This emphasizes the unpredictability of diazepam respiratory depression (Buskop, Price and Molner, 1967; Hunter, 1967) in the presence of other anaesthetic agents.

A high mortality rate is associated with agenesis of the corpus callosum when the symptoms present in infancy (Slager, Kelly and Wagner, 1957; Shapira and Cohen, 1973). This is the result of other severe congenital defects affecting many systems (Slager, Kelly and Wagner, 1957). There is frequently clinical evidence of a diffuse neurological deficit (Carpenter and Druckenmiller, 1953) and the abnormal brain development leads to a reorganization of neural pathways linking the cortex and limbic system (Ettlinger et al., 1972). The pneumoencephalogram confirmed the absence of the corpus callosum and this may have contributed to the relative failure of ketamine anaesthesia. However, it is likely that other associated anomalies, including a cystic lesion of the right cerebral hemisphere and hydrocephalus, played a significant part by further disrupting normal neural pathways. It would appear that if, as a result of fundamental neural reorganization, abnormal pathways link the cortex and limbic system, ketamine may not provide adequate analgesia.

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KETAMINE ET AGENESIE DU CORPS CALLEUX

RESUME

La kétamine n'a pas provoqué l'anesthésie appropriée lors d'une pneumoencéphalographie chez un enfant âgé de 10 semaines, atteint d'une agénésie du corps calleux. Il est vraisemblable que la raison de cet échec provienne d'anomalies neurologiques associées.

KETAMIN UND OVARIALAPLASIE DES GEHIRNBALKENS

ZUSAMMENFASSUNG

Ketamin war als Narkosemittel für Pneumoenzephalographie bei einem 10wöchigen Kind mit Ovarialaplasie des Gehirnbalkens nicht ausreichend. Ein wahrscheinlicher Grund fur dieses Versagen besteht in vorhandenen neurologischen Defekten.

QUETAMINA Y AGENESIA DEL CUERPO CALLOSO

SUMARIO

La quetamina no proveyó una anestesia adecuada para la neumoencefalografía de un niño de 10 semanas con agenesia del cuerpo calloso. Los defectos neurológicos asociados constituyeron muy probablemente la causa de esta deficiencia.

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A MODIFICATION OF THE MGA 200 MASS SPECTROMETER TO ENABLE MEASUREMENT OF ANAESTHETIC GAS MIXTURES

W. O. M. DAVIS AND A. A. SPENCE

SUMMARY

The measurement of anaesthetic gas mixtures with a mass spectrometer is complicated by the overlap of fragmentation products of the anaesthetics with the normal respiratory gas. For the MGA 200 quadrupole instrument the problem has been overcome by incorporating simple circuitry which, for an appropriate mass number, sums the concentrations of the unwanted fragments and subtracts them from the total output for the particular channel; this provides an accurate and stable system (within ± 1% f.s.d.) over at least 24 h.

Mass spectrometers for gas analysis in clinical practice are capable of measuring the partial pressures of several gases simultaneously with a response time of less than 100 ms and total channel scan time of 20 ms. In recent years we have had available for respiratory investigation the MGA 200 (Centronic Limited, Croydon), capable of accurate measurement of nitrogen, oxygen, carbon dioxide and argon. It has an automatic stability control mode (ASC) which expresses the partial pressures of each gas present (excluding water vapour) as a proportion of the total mixture (100%). Used in this manner, it has proved to be reliable having a stability of ± 1% (f.s.d.) over 24 h. In anaesthesia, however, where the gas mixture may include nitrous oxide and halothane, it is not possible to use the MGA 200 in the ASC mode because of interference caused by overlapping spectra produced by the fragmentation of the gas components. It is possible to set the MGA 200 to read gas mixtures of oxygen, carbon dioxide, nitrous oxide, argon and halothane and operate without ASC, but at best there is a drift of approximately ± 4% per hour.

We have developed a system (a spectrum overlap eraser, SOE) to remove the interference caused by overlapping spectra and which allows the ASC mode to be used with anaesthetic gas mixtures with, in addition, a notable improvement in stability. The SOE is a four-channel, three-input per channel, system (fig. 1) utilizing simple analog operational amplifier computing techniques which enable it continuously to add, subtract, multiply and divide the MGA 200 outputs, removing the unwanted spectra overlap. The interference-free outputs are fed back to the ASC circuit, allowing it to perform to its ASC mode specification.

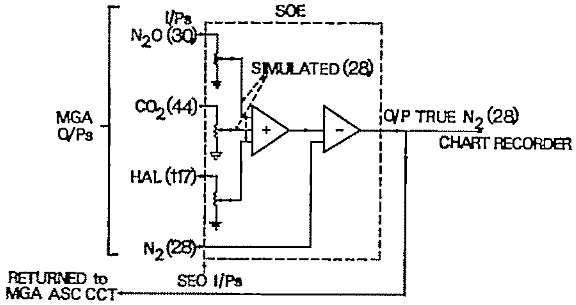

FIG. 1. Spectrum overlap eraser (SOE) circuitry. ASC = automatic stability control; CCT = circuit; I/P = input; O/P = output.

METHODS

The spectrum of each gas or vapour of interest was obtained by analysing nominal 100% gases (BOC Medical Gas specification) in the MGA 200. It was evident that N_2 on mass 28, O_2 on mass 32, CO_2 on mass 44 and N_2O on mass 30 would be affected by a mixture containing N_2O, CO_2 and halothane. For example, a mixture of 10% N_2, 36% O_2, 9% CO_2, 32% N_2O, 13% Ar, read: 14.5% N_2, 38% O_2, 30% CO_2, 32% N_2O, 13% Ar. The N_2 output was increased by the contribution of mass 28 from CO_2 and N_2O; the O_2 output by mass 32 from N_2O; CO_2 output by mass 44 from N_2O, and so on. From the above example it can be seen that the "sum" of the gases measured exceeded 100% (approximately 127%). Had the MGA 200 been operated in the ASC mode, the output would be compressed to 11.4% N_2, 29.8% O_2, 23.5% CO_2, 25.1% N_2O, 10.2% Ar.

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As the ratio between fragmentation peaks is constant for any one gas or vapour, for more than 24 h, circuitry was developed into which this ratio could be set; as more than one gas was being analysed, circuitry to add the undesired fragmentation peaks and subtract them from the inflated reading from the MGA 200 enabled the erroneous reading from the mass spectrometer to be corrected to read the true value of the gas analysed. Therefore, in the case of N_2 measured on mass 28 in the presence of N_2O on mass 30 (fig. 1) the N_2O output, if fed into the potential divider circuit set to the ratio of peak 30 to peak 28, will give a continuous signal for mass 28 which is interfering with the N_2 reading. If the potentiometer output is then fed to a subtraction circuit and is subtracted from the mass 28 output attributable to N_2 plus the interference from N_2O, the output signal from the subtractor will signify the true amount of N_2 in the mixture. When N_2 is to be measured in the presence of N_2O mass 30, CO_2 mass 44 and halothane mass 117, the ratio between their measured peaks and peak 28 is set in the divider circuits, their outputs are added in the adder circuit and subtracted from the inflated 28 peak to read the true N_2 percentage in the mixture.

Having abolished the spectra overlap, it is possible with simple modification to feed the SOE outputs to the MGA 200 ASC summing circuit, enabling it to operate in the ASC mode.

CALIBRATION

Calibration can be achieved by two methods. The ratio between wanted and unwanted peaks can be measured and dialled into the digital potentiometer divider circuits. The MGA is calibrated from one or two accurate gas mixtures (BOC Gold Star). However, this method relies on the shape of the peak remaining constant.

In routine practice, calibration can be obtained by using medical grade gases; for example, 100% N_2O will produce a wanted peak at mass 30 and unwanted peaks at mass 28, 32 and 44. With the mass 30 peak adjusted to read 100%, the unwanted peaks can be reduced to zero by increasing the potentiometer setting associated with that peak, hence abolishing the overlap caused by N_2O on the N_2, O_2 and CO_2 channels. Similarly, spectra overlap attributable to O_2, CO_2 and halothane is overcome. The MGA is then switched to ASC mode and the calibration checked with a suitably certificated gas mixture (BOC Gold Star).

Careful calibration can produce measurement of the components of a N_2, O_2, CO_2, N_2O, Ar and halothane mixture to within 1% of the value for each gas and will maintain this accuracy for more than 24 h.

The present system with its four-channel, three-input per channel capability could, with ease, be extended to a six-channel, six-input per channel system capable of coping with trichloroethylene and enflurane.

MODIFICATION DU SPECTROMETRE DE MASSE MGA 200 PERMETTANT LA MESURE DES MELANGES DE GAZ ANESTHESIANTS

RESUME

La mesure des mélanges de gaz anesthésiants, à l'aide d'un spectromètre de masse, est rendue plus difficile par le chevauchement des produits de fragmentation des anesthésiques et des gaz respiratoires normaux. On a pu surmonter les difficultés rencontrées avec l'instrument quadripolaire MGA 200, en y incorporant un ensemble de circuits simples qui permet, pour un nombre de masse approprié, d'additionner les concentrations des fragments indésirables et de les soustraire du débit total pour la bande en question. On obtient ainsi un système stable et précis (dans les limites de ±1% de déviation maximale) sur une période d'au moins 24 h.

EINE MODIFIZIERUNG DES MASSENSPEKTROMETERS MGA 200, UM NARKOSEGASMISCHUNGEN MESSEN ZU KÖNNEN

ZUSAMMENFASSUNG

Die Messungen von Narkosegasmischungen mittels Massenspektrometer sind kompliziert aufgrund der Überlagerung von Partikeln des Narkosemittels mit dem normalen Atmungsgas. Bei dem vierpoligen Instrument MGA 200 wurde dieses Problem durch Aufnahme einer einfachen Schaltung überwunden, die für eine entsprechende Massenzahl die Konzentrationen der unerwünschten Partikel summiert und sie dann von der Gesamtleistung des betreffenden Kanals subtrahiert. Dies gewährleistet ein genaues und stabiles System (Genauigkeit ±1%) über wenigstens 24 Stunden.

UNA MODIFICACION DEL ESPECTOMETRO DE MASA MGA 200 PARA PERMITIR MEDICIONES DE LAS MEZCLAS DE GASES ANESTETICOS

SUMARIO

Se complica la medición de mezclas de gases anestéticos con un espectómetro de masa a raíz de la superposición de los productos de fragmentación de los anestéticos con los gases respiratorios normales. En el instrumento cuadripolar MGA 200, se solucionó el problema al incorporarle un simple sistema de circuitos que, para un número de masa apropiado, suma las concentraciones de los fragmentos indeseados y los sustrae de la producción total del canal en cuestión; esto provee un sistema exacto y estable (dentro de ±1% f.s.d.) durante 24 h por lo menos.

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PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

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EFFECT OF KETAMINE ON TRANSMISSION IN SYMPATHETIC GANGLIA

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An increase in arterial pressure following the injection of ketamine is well documented and has been explained by both central (Ivankovich et al., 1974) and peripheral actions (Nedergaard, 1973). The sympathetic division of the autonomic nervous system is the link between central and peripheral mechanisms for increasing arterial pressure. It was therefore decided to investigate the effects of ketamine on this final common pathway.

The hypogastric nerve, hypogastric plexus and vas deferens of adult guineapigs were dissected (Hukovic, 1961) and mounted in Krebs' solution bubbled with oxygen 95% and carbon dioxide 5% at 32 °C. Supramaximal transmural (postganglionic) and nerve stimuli (preganglionic) were applied alternately and contractions of the vas deferens were measured using an isotonic transducer.

The concentration of ketamine in the bath was increased at 16-min intervals. The effect of each concentration was expressed as a percentage of the control response. For comparison, the effect of hexamethonium was also studied. Ketamine produced a dose-dependent reduction in the response to preganglionic stimulation (IC_{50} 2.05×10^{-4} mol litre^{-1}, $r = 0.9$), but did not reduce the response to post-ganglionic stimulation. The response to post ganglionic stimulation was blocked by guanethidine 1×10^{-4} mol litre^{-1}.

The preganglionic electrodes in this study were placed considerably proximal to the ganglionic synapse, and it was necessary therefore to confirm that ketamine was acting as a nicotinic blocking agent rather than as a non-specific depressant of nerve action potentials. Experiments were performed using the frog (*Rana temporaria*) rectus abdominis muscle. The muscle was mounted in frog's Ringer solution bubbled with air at 18 °C.

The contraction of the muscle in response to carbachol 5.46×10^{-7}–1.6×10^{-5} mol litre^{-1} was measured. The contractions of the preparation in the presence of carbachol in the same concentrations with ketamine 1×10^{-4} mol litre^{-1} were recorded also. Ketamine caused a reversible depression of the response to carbachol. The response of the preparation to potassium chloride 3.3×10^{-2} mol litre^{-1} was unchanged by ketamine.

The muscle contraction produced by carbachol 5.46×10^{-6} mol litre^{-1} in the presence of increasing concentrations of ketamine was also studied. Ketamine produced a dose-dependent reduction in the contraction produced by carbachol. The concentration of ketamine which produced a 50% depression in the response to carbachol 5.46×10^{-6} mol litre^{-1} was determined (IC_{50} ketamine $= 8.5 \times 10^{-5}$ mol litre^{-1}, $r = 0.83$).

In the concentrations used ketamine has been shown to interfere with the sympathetic final common pathway but the results do not preclude a central effect at lower concentrations.

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EFFECTS OF KETAMINE ON AUTONOMIC TRANSMISSION IN RAT ISOLATED ATRIA

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It is well recognized that ketamine stimulates the heart. Adams, Parker and Mathew (1977) showed that ketamine changed the response of isolated atria to catecholamines, but interactions between autonomic neurotransmission and ketamine have not been studied *in vitro*. The present study was designed to investigate the effects of ketamine on the response of rat atria to stimulation of the autonomic nerve supply and to exogenous catecholamines.

Atria were removed from freshly killed Wistar rats (300–450 g). Each atrium was suspended between parallel platinum wire electrodes in an organ bath containing Krebs' solution gassed with 95% O_2 and 5% CO_2 at 37 °C. The left atrium was paced at 3 Hz by field stimulation (10-V, 2-ms pulses) to study inotropic changes. The right atrium was allowed to beat spontaneously and used to study chronotropy. Noradrenergic nerves in both atria were stimulated in the presence of atropine 1×10^{-6} mol and left atrial cholinergic nerves in the presence of propranolol 1×10^{-6} mol according to the method of Blinks (1966). This gave graded chronotropic responses to different frequencies of stimulation (2–20 Hz) from the right atrium and a single inotropic response to the pacing frequency from the left atrium.

Ketamine 5×10^{-5} mol increased the maximum amplitude of the inotropic response of the left atrium to noradrenergic nerve stimulation ($P < 0.01$). The duration of the response was also markedly enhanced. In a concentration of 4×10^{-4} mol, ketamine caused a slight increase in resting force of contraction but a significant ($P < 0.001$) decrease in the positive inotropy seen in response to noradrenergic nerve stimulation.

Ketamine produced a dose-dependent slowing of the right atrium. The control rate of 284 ± 4 beat min^{-1} decreased to 155 ± 5 beat min^{-1} in the presence of ketamine 4×10^{-4} mol. This masked the effects of ketamine on the positive chronotropic response to noradrenergic nerve stimulation.

Ketamine, in concentrations up to 4×10^{-4} mol, decreased the negative inotropic response to cholinergic nerve stimulation in left atria but this effect was unrelated to the ketamine concentrations used.

The effects of ketamine on the responses of left atria to exogenous noradrenaline and isoprenaline were studied. Potentiation of the response of the left atrium to noradrenaline by ketamine 5×10^{-5} mol was seen as a parallel leftward shift of the noradrenaline dose–response curve (threefold increase in potency) with no increase in the maximum response. In a concentration of 2×10^{-4} mol, ketamine depressed the maximum response to noradrenaline. Ketamine 5×10^{-5} mol also potentiated the response of the left atrium to isoprenaline (twofold increase in potency).

Ketamine has therefore been shown to increase the inotropic response both to noradrenergic nerve stimulation and to exogenous noradrenaline. This is consistent with the hypothesis that ketamine causes a postjunctional sympathomimetic super-sensitivity combined with an increase in the available noradrenaline as a result of blockade of neuronal re-uptake which has been reported by Miletich and others (1973).

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THE DEVELOPMENT OF THE MGA 200 MASS SPECTROMETER FOR CLINICAL USE IN ANAESTHESIA

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Mass spectrometry is well established in respiratory investigation but its application in anaesthesia is more complex because of interference by fragmentation products of substances including nitrous oxide and halothane with the signals from nitrogen, oxygen and carbon dioxide.

As the ratio of fragmentation peaks is constant for any gas or vapour for a period of at least 24 h, simple circuitry has been developed into which this ratio can be set for the MGA 200 quadrupole apparatus (Centronic Limited, Croydon); circuits to add the undesired fragmentation peaks and subtract them from the apparent, but erroneous, reading allow the true value of the gas to be analysed. The outputs of these circuits can be fed to the MGA 200 automatic stability control mode (ASC) circuit providing stability of calibration of $\pm 1\%$ (full scale-deflection) for each gas or vapour for more than 24 h.

Mass spectrometers are unlikely to be of value in clinical anaesthesia unless one instrument can be shared between several anaesthetizing locations. We have demonstrated that gas can be sampled over distances of 40 m (sample flow 25 ml min^{-1}) without serious loss of the respiratory waveform; the 90% rise time using a conventional 1-m probe was 80 ms^{-1} but increased to 500 ms^{-1} with a 40-m probe. The patient to mass spectrometer transit time was approximately 30 s. A shared facility between four operating theatres allows analysis of at least two b.p.m. for each patient.

MEASUREMENT OF BLOOD-GAS TENSIONS BY MASS SPECTROMETRY—THE "SUPER RILEY BUBBLE"

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If a small bubble of gas is equilibrated with a sample of blood at body temperature, the final partial pressures of gas in the bubble approximate to the initial tensions in the blood. This principle, with chemical analysis of the bubble, was used by Riley, Proemmel and Franke (1945) for the determination of O_2 and CO_2 tensions. In the present technique analysis by a respiratory mass spectrometer (Centronic MGA 200) was used to determine the tensions of halothane and CO_2 in arterial blood from dogs breathing a mixture of halothane and nitrous oxide in oxygen.

A 5-ml all-glass syringe, modified to provide a conical deadspace of about 0.2 ml and fitted with a nylon three-way tap, was flushed with the mixture which was delivered to the dog via a halothane vaporizer. The syringe was filled with 2 ml of arterial blood and rotated in a water bath at body temperature in such a way that the bubble travelled to and fro inside the syringe for 2 min. The plunger moved freely to ensure the maintenance of atmospheric pressure in the bubble. The needle of a 100-µl syringe was inserted through the tap into the gas bubble and a 100-µl sample drawn up. This was injected deep into a wide-bore needle through which the mass spectrometer was continuously sampling room air. The resulting transient changes in gas composition were sensed by the mass spectrometer and processed by an on-line digital computer to yield an analysis of the bubble.

Theory indicates that, at equilibrium, the partial pressures of halothane and CO_2 in the bubble should be only 2–3% smaller than the initial tensions in the blood; for N_2O there may be variation over a range of 10% of the initial tension; and the oxygen partial pressure makes up the total atmospheric pressure virtually irrespective of the initial blood oxygen tension.

Experiments showed that the components of a 100-μl sample of *dry* gas could each be measured to an accuracy of the order of 2%; but for bubbles equilibrated with tonometered blood the halothane and CO_2 partial pressures were smaller than predicted to a variable degree. This shortfall could not be attributed to incomplete equilibration; it may have been a result of re-equilibration of the bubble with traces of blood in the 100-μl syringe and wide-bore needle. Experiments showed that, with correction for the systematic error, halothane and CO_2 tensions in dog blood could be measured with SD about 5%.

ACKNOWLEDGEMENT

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ANAESTHETIC CONTAMINATION IN DIFFERENT TYPES OF HOSPITAL

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A large number of studies on anaesthetic contamination have been published which support the common-sense conclusion that at least some precautions should be undertaken to reduce the ambient concentrations of anaesthetic. Unfortunately, many of the studies (including one from our institution; Davenport et al., 1976) have been carried out in modern hospitals under controlled, contrived or "ideal" conditions. This makes it difficult to extrapolate such data to the routine conditions existing in many hospitals. In this paper we report anaesthetic measurements in operating room areas of 20 hospitals during normal unmodified operating sessions. We chose our minimum detectable limits as 10 p.p.m. of nitrous oxide and 0.1 p.p.m. halothane and standardized our collection procedure in each hospital, using an integrated personal sampler (Davenport et al., 1976). The following areas were studied:

1. *Induction room*: In the periphery of an induction room during induction of anaesthesia for 10 min.
2. *Theatre periphery*: On the periphery of the operating theatre during an anaesthetic, for 30 min.
3. *Anaesthetists' area*: Within 40 cm of the head of the patient in the operating room at the level of the anaesthetist's nose, for 10 min.
4. *Anaesthetist's session*: Continuous sampling from the front of the mask of the anaesthetist during his varied activities over a duration of 2 h.
5. *Recovery room*: In the periphery of the recovery room with one or more patients in the room.

Finally, in Northwick Park Hospital, we sampled in an exactly similar manner on 5 consecutive days without a scavenging system in operation. This was followed by sampling for 5 days with routine scavenging by a system we have employed for over 2 years.

Overall results from 19 hospitals are shown in table I. The detailed data with and without scavenging at Northwick Park Hospital will be presented. Comparisons between these results indicate that the installation of relatively simple active scavenging devices will probably be effective in most hospitals.

Table I. *Mean anaesthetic contamination (and range) for 19 hospitals*

	N_2O (p.p.m.)	Halothane (p.p.m.)
Induction room	187 (30–540)	1.9 (<0.1–6.3)
Theatre periphery	171 (50–670)	1.3 (<0.1–3.1)
Anaesthetist's area	189 (60–650)	2.0 (<0.1–7.1)
Anaesthetist's session	381 (75–1100)	3.1 (<0.1–16.9)
Recovery room	30 (<10–110)	0.43 (<0.1–1.8)

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DIFFERENTIATION OF THE MOLECULAR SITES FOR ANAESTHESIA AND PRESSURE

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The multi-site expansion hypothesis (Halsey, Wardley-Smith and Green, 1978) has been proposed as an explanation for the pressure reversal of anaesthesia. One aspect of this hypothesis is that high pressure may act at a different molecular site from the anaesthetic; also for a particular anaesthetic, one site may predominate in determining the characteristics of their interaction.

Evidence for this idea is provided by differences between anaesthetics in their ability to protect against the high pressure nervous syndrome (HPNS). It was originally thought that all anaesthetics would be equally effective in preventing adverse physiological changes induced by pressure, but we have shown that this is not so. In rats, the convulsion threshold is accepted as a reproducible end-point for studying HPNS, and results for six different anaesthetics are shown in table I.

The use of structural isomers of anaesthetics is an approach which may make it possible to distinguish between separate molecular receptors for anaesthesia and pressure. Alphaxalone, the main constituent of Althesin, has isomers including Δ16-alphaxalone and 3β-hydroxyalphaxalone which, although differing only slightly in structure, are completely "non-anaesthetic". If a non-anaesthetic isomer of alphaxalone protected against HPNS, this would be further positive evidence of separate receptors for anaesthetics and pressure, and preliminary results support this.

It is probable however that these receptors are linked, since preliminary screening of a range of non-anaesthetic anticonvulsants in mice have not indicated that this type of drug will be of any value in treating pressure-induced convulsions. In view of all these data, it seems likely that there is some interaction between the separate sites for anaesthesia and pressure.

TABLE I. *Convulsion and tremor thresholds expressed in atmospheres absolute (atm) for six different anaesthetics*

Anaesthetic	Convulsion threshold (atm ± SEM)	Tremor threshold (atm ± SEM)
Control	76.8 ± 2.0	37.1 ± 2.5
Althesin	> 100	73.4 ± 3.1
Methohexitone	46.4 ± 2.6	27.8 ± 3.7
Thiopentone	79.0 ± 3.9	42.7 ± 5.8
Propanidid	58.2 ± 2.4	42.7 ± 3.3
Ketamine	> 100	> 100
Nitrous oxide	> 100	> 100

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THE INFLUENCE OF DIET ON THE SUSCEPTIBILITY OF *XENOPUS LAEVIS* TADPOLES TO THIOPENTONE AND A MEMBRANE PROBE

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Anaesthetics can selectively perturb lipid bilayer membranes (Miller and Pang, 1976). The physical nature of a membrane may be modified by altering the nature of its phospholipid molecules (Van Deenan, De Grier and Demel, 1972). In addition, there is evidence that the nature of the fatty acids in the phospholipids of the membrane bilayer may be altered by the media or food which is available to the cells or animals concerned (Burns et al., 1977).

Xenopus laevis tadpoles were produced from wild-caught, laboratory-reared toads, following induced mating and spawning. Separate groups were fed on diets of: (1) liver powder; (2) nettle powder; or (3) aminosol and intralipid. The tadpoles were reared for 3 weeks at 22 °C and then numerous experiments were performed.

Group 1 experiments compared tadpoles reared on nettle powder and liver powder. Equal numbers of both groups of tadpoles were placed in 200 ml of free-standing water and 1 mg of thiopentone dissolved in 0.5 ml of water was added sequentially until all the tadpoles were motionless and unresponsive to touch. The experiments were repeated in Darrow's solution.

Group 2 experiments compared tadpoles reared on liver powder, nettle powder, or aminosol and intralipid. Equal numbers of tadpoles from each group were exposed to selected doses of thiopentone and dose-response curves were constructed. These experiments were carried out in 200 ml of standing water and thiopentone was said to be 100% active when all the tadpoles were immobile.

Group 3 experiments compared tadpoles reared on liver powder and aminosol and intralipid. A fluorescent membrane probe was tested to see if it possessed anaesthetic activity and was influenced by the diet of the tadpoles. These experiments followed exactly the same pattern as Group 2, except that they were carried out in 100 ml of standing water.

In Group 1 experiments there was a significant difference in the response of the two groups of tadpoles to thiopentone (statistical analysis by Wilcoxon's sum of ranks test and the binomial expansion of Bernouilli).

In Group 2 experiments there was a difference in response which did not result from kinetic factors. The shift in the dose-response curve between the nettle- and liver-fed groups appeared to result from a competitive reaction but non-competitive factors seemed to be present for the intralipid group.

In Group 3 experiments the differences in response to the membrane probe were more pronounced.

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THE EFFECT OF HALOTHANE AND ENFLURANE ON SPECIFIC AIRWAYS CONDUCTANCE IN MAN

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Rügheimer, Himmler and Greiner (1974) reported that enflurane increased airways resistance (*R*aw) whereas Rolly and Malcolm-Thomas (1975) found that both enflurane and halothane caused a reduction in *R*aw. Changes in lung volume during anaesthesia profoundly affect *R*aw (Lehane, Jordan and Jones, 1979). However, neither Rügheimer and colleagues nor Rolly and Malcolm-Thomas allowed for the effects of changes in lung volume and this omission may account for the differences in their results.

We have used the forced airflow oscillation method (Lehane, Jordan and Jones, 1979) to determine airflow resistance over a range of lung volumes during anaesthesia. The resulting hyperbolic plot of resistance against lung volume can be redrawn after correcting for the asymptote to yield a linear plot of conductance against volume. The slope of this line, the specific airways conductance (s*G*aw), is independent of changes in lung volume. Changes in s*G*aw therefore reflect changes in bronchomotor tone. We have measured the change in s*G*aw when halothane 1.3% or enflurane 2.5% was added during light nitrous oxide anaesthesia.

Patients were allocated randomly into two groups of 10, one group receiving halothane, the other enflurane. All patients were non-smokers. Premedication was with oral diazepam 15 mg/70 kg. Following thiopentone and pancuronium, anaesthesia was maintained with 70% nitrous oxide and ventilation adjusted to give a $P\mathrm{E}'_{\mathrm{CO}_2}$ of 5 kPa. During this period of light nitrous oxide anaesthesia at least three measurements of s*G*aw were made. Halothane or enflurane was added to the inspired gas mixture and further measurements of s*G*aw were obtained 3, 8, 15 and 25 min later. End-tidal concentrations of these agents were measured continuously using a mass spectrometer. At 15 min the range of end-tidal concentrations of both agents was 0.76–0.93 MAC. Measurements of s*G*aw during light nitrous oxide anaesthesia showed a skewed distribution which was normalized by taking logarithms. This permitted the application of the paired *t* test.

Following addition of halothane, s*G*aw increased significantly in each of five patients ($P < 0.05$, two-sample *t* tests), mean values increasing from 7.5 to 19.4 $\mathrm{kPa}^{-1}\,\mathrm{s}^{-1}$, and decreased in one patient from 6.3 to 4.8 $\mathrm{kPa}^{-1}\,\mathrm{s}^{-1}$ ($P < 0.02$). In four patients there was no significant change.

Following addition of enflurane s*G*aw increased from 9.8 to 18.4 $\mathrm{kPa}^{-1}\,\mathrm{s}^{-1}$ in three patients ($P < 0.05$). There were no significant changes in seven patients.

The average change after 15 min of halothane was an increase in s*G*aw of 60% (n.s.: $P = 0.09$, paired *t* test) and after enflurane there was an increase of 43% ($P < 0.02$).

In conclusion, the majority of these patients responded to both of these agents with bronchodilatation, and there was no evidence that enflurane was more likely to induce bronchoconstriction than halothane.

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A NEW METHOD FOR MEASURING ALVEOLAR EPITHELIAL MEMBRANE PERMEABILITY IN MAN

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An increase in permeability of the alveolar epithelial membrane (AEM) is believed to be initiated by a large variety of processes associated with the development of the adult respiratory distress syndrome. There is no suitable method available for the early diagnosis of an increase in permeability of the AEM in man. The diagnosis can be made only at a very late stage from radiological evidence of pulmonary oedema when the pulmonary artery wedge and plasma colloid osmotic pressures are normal. We have developed a simple technique to obtain an index of AEM permeability in animals (Jones et al., 1978) and we now report a development of this technique for use in man. An aerosol of the hydrophilic molecule $^{99\mathrm{m}}$Tc DTPA (mol. wt 452 dalton) in saline was generated using a disposable "Acorn" nebulizer and a settling bag to remove particles greater than 2.0 μm in size (Taplin and Chopra, 1978). Male staff volunteered to be subjects for the study. After breathing the aerosol for 3 min, the disappearance rate of the isotope from the lung was derived using two scintillation detectors, one over the rib cage and the other over the thigh. The latter was used to correct for the increasing activity of $^{99\mathrm{m}}$Tc DTPA extracted from the lung into the circulation. The two curves were analysed to produce a mono-exponential lung clearance curve. Seven subjects who were non-smokers had a mean lung clearance $T_{\frac{1}{2}}$ of 72.4 ± 7.4 min (SEM), whereas 11 cigarette smokers had a mean clearance $T_{\frac{1}{2}}$ of 27.0 ± 6.2 min (SEM) ($P < 0.001$). We have also studied three patients (non-smokers). Two with pulmonary oedema following myocardial infarction had $T_{\frac{1}{2}}$ of 88 min and 49 min, and one with permeability pulmonary oedema from systemic lupus had a $T_{\frac{1}{2}}$ of 32 min.

These results indicate that AEM permeability is increased in symptomless cigarette smokers but it is not known how this effect is mediated. Because of relatively low molecular weights of $^{99\mathrm{m}}$Tc DTPA the test provides a sensitive index of early alveolar epithelial damage. In non-smokers a rapid clearance may suggest the presence of a pathological process predisposing to pulmonary oedema, but the addition to the test of a measurement of the clearance of a second marker of larger molecular weight would improve its value in predicting the development of permeability pulmonary oedema in smokers and non-smokers.

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FRESH GAS AND VENTILATORY REQUIREMENTS DURING CONTROLLED VENTILATION WITH T-PIECE SYSTEMS

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Measurements during controlled ventilation of gas composition within the corrugated tubing of both conventional and coaxial D systems have shown considerable longitudinal mixing of fresh and expired gas along the system. If a uniform mix of these gases is assumed and if carbon dioxide output ($\dot{V}\mathrm{CO}_2$) and $V\mathrm{D}/V\mathrm{T}$ are assumed to be constant, the prevailing CO_2 will be a function of fresh gas flow, [$\dot{V}\mathrm{F}$], minute ventilation, $V\mathrm{E}$, and the character of the inspiratory waveform.

Based on these assumptions, theoretical analyses have been performed using square, sinusoidal, exponential and a variety of triangular inspiratory waveforms. The resulting predicted values of $F_{A_{CO_2}}$ at various values of $\dot{V}_F$, V_E and $\dot{V}_{CO_2}$ have been assessed in relation to a previous study in which dogs were ventilated to an acute steady state using a Bain system and a variety of values of $\dot{V}_F$ and V_E (Seeley, Barnes and Conway, 1977). The predicted data for square wave inspiration agree closely with the observed data ($r = 0.98$). It is suggested that in practical use the optimal values of $\dot{V}_F$ and V_E to provide normocapnia are in the order of 1.25 and 1.5 times the basal (anaesthetized) minute volume respectively. In adult man this would entail a $\dot{V}_F$ of 100 ml^{-1} kg^{-1} min^{-1} and a V_E of 120 ml^{-1} kg min^{-1}.

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ENFLURANE IN A CLOSED CIRCLE-ABSORBER SYSTEM; VAPORIZER INSIDE THE CIRCLE

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As an approach to the problems of pollution, economy and in seeking an alternative to halothane, we have investigated the use of enflurane in a closed anaesthetic system. The Marrett apparatus, which incorporates an in-circle vaporizer (VIC), was used.

Ten healthy adult patients undergoing orthopaedic or plastic surgical procedures on one or more limbs gave informed consent for the study. Premedication consisted of levorphanol 1.5–2.0 mg, promethazine 25 mg and hyoscine 0.3–0.4 mg i.m., 1 h before surgery. In the anaesthetic room a central venous catheter was inserted and the leads of a cerebral function monitor (CFM) were attached. Anaesthesia was induced with gallamine 20 mg, thiopentone 250–500 mg and suxamethonium 100 mg i.v., followed by topical analgesia with 4% lignocaine to the larynx and trachea. The lungs were inflated with 100% oxygen before passage of an Enderby-type endotracheal tube containing a sampling catheter. The fresh gas flow was set at 250–300 ml of 100% oxygen and initially the vaporizer was set to mark 8 (maximum—patient's breath only). The system was closed and ventilation allowed to return spontaneously.

Using the endotracheal sampling catheter, end-tidal carbon dioxide concentration was measured with a Hartmann and Braun infra-red carbon dioxide analyser. In addition, peak inspired and end-tidal enflurane concentrations were measured using an infra-red Miran 1a analyser. The sampled gases (approximately 0.5 litre min^{-1}) were returned, after analysis, to the expiratory limb of the circle. The outputs of both infra-red analysers were fed continuously into a two-channel recorder (Devices). Tidal and minute volumes were measured using a Wright's respirometer connected to a digital display. Systemic arterial pressure and heart rate were measured during and after operation with an oscillotonometer.

With the vaporizer on mark 8, end-tidal enflurane concentration varied from 1.5 to 3% and inspired concentration from 2.5 to 5%. One patient exhibited intermittent sighing respiration throughout. End-tidal enflurane concentrations in excess of 2% were associated with a reduced tidal volume and increased end-tidal concentration of carbon dioxide.

Heart rates were within normal range and no arrhythmias were detected. Arterial systolic pressure measurements were in the low to normal range (90–110 mm Hg). The CFM traces varied greatly. Some exhibited a depth-related decrease in trace position and two exhibited marked, persistent burst-suppression, which disappeared only with reduction in concentration of enflurane. Time taken for spontaneous recovery after operation varied from 25 to 80 min. The volume of liquid enflurane used was between 10 and 15 ml h^{-1}.

It is concluded that enflurane can be administered with oxygen in a closed-circuit system using a VIC. However, cerebral and respiratory depression may be marked and not easily detected clinically. Therefore, monitoring of cerebral function and end-tidal enflurane and carbon dioxide concentrations would appear to be proper safeguards.

INABILITY TO MAINTAIN VENTILATION AGAINST LARGE INSPIRATORY THRESHOLD LOADS: MUSCLE FATIGUE OR PROGRESSIVE FAILURE OF CO-ORDINATION?

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Respiratory muscle fatigue may be an important cause of failure to wean patients from mechanical ventilation. Roussos and Macklem (1977) have reported that diaphragmatic fatigue occurs in normal subjects during inspiratory loading when the transdiaphragmatic pressure (*P*di) persistently exceeds 40% of maximum. They used a difficult manœuvre to control *P*di and we have simplified the manœuvre by using inspiratory threshold loads. We have examined changes in respiratory muscle function in five subjects breathing against these loads by measuring pleural pressure (*P*pl), gastric pressure (*P*gast), mouth pressure, end-tidal CO_2 and tidal volume. In two subjects the amplitude of AP movements of abdomen/diaphragm (A/D) and rib cage (RC) were monitored with magnetometers.

We observed that: (1) Breathing could not be maintained indefinitely when the load exceeded 60% of maximum negative *P*pl. Above this load there was an inverse relationship between duration of ventilation and load. (2) There was disco-ordination of movement of the chest wall upon initiating high load breathing identified by (a) asynchrony of a *P*gast *v*. *P*pl plot leading to eventual cessation of change of *P*gast; (b) the magnetometer measurements which showed that during inspiratory effort, but before gas flow, A/D and RC were opposite in phase while, during gas flow, they tended to come into phase. As ventilation became more difficult to sustain there was progressive diminution in amplitude to the A/D component. (3) There was an abrupt decrease of lung volume on loading inspiration, shown by an increase in end-expiratory *P*pl, a reduction in ERV, and from the magnetometer signals. As subjects experienced increasing difficulty in maintaining loaded breathing, there was a further decrease in ERV almost to RV.

When the load became intolerable, the subject was allowed a single unloaded breath (SUB) before resuming loaded breathing. Immediately following this breath, the *P*pl/*P*gast plot, the A/D–RC movement and the ERV were all restored to the non-fatigue state seen soon after initial loading, and this transient unloading permitted a further prolonged period of loaded breathing, the duration of which was a function of the magnitude of the load.

The ability of the respiratory muscles to sustain ventilation at high levels of load was compared with the ability of the biceps muscle to support loads. When the biceps muscle was intermittently loaded at 80% of its maximum load-carrying capacity by 3-s contractions (12/min), it showed a repeatable time to fatigue. In contrast with loaded breathing, a 5-s rest period at the fatigue point was followed by only a brief recovery of ability to maintain load (table I).

TABLE I. *Mean time to "fatigue" ± 1 SD (s)*

	Inspiratory load 80% *P*pl max	After SUB	Biceps load 80% max	After 5 s rest
Subject (1) (J. G. J.)	265 ± 17	110 ± 12	227 ± 42	19.0 ± 3.6
Subject (2) (P.L.)	249 ± 26	61 ± 17	195 ± 13	18.3 ± 3.5

We concluded that inspiratory musculature fails to maintain ventilation when inspiratory loading exceeds 60% of maximum negative *P*pl and that this results predominantly from a failure of co-ordination which may be restored immediately when loaded breathing is resumed after a single unloaded breath. This may be the mechanism by which intermittent mandatory ventilation could exert a beneficial effect during weaning from mechanical ventilation.

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THE SYSTEMIC HAEMODYNAMIC EFFECTS OF MINAXOLONE: A COMPARISON WITH OTHER ANAESTHETICS IN THE DOG

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Minaxolone is a water-soluble steroid anaesthetic with properties similar to those of alphaxalone in animals and man (Aveling et al., 1979; Davis et al., 1979). We have compared haemodynamic responses in the dog to induction of anaesthesia with minaxolone, thiopentone, methohexitone and etomidate.

Six beagle dogs (weight range 10.2–13.0 kg) were subjected to left lateral thoracotomy. An electromagnetic flow transducer was placed around the ascending aorta and a Konigsberg P6.5 pressure transducer was inserted into the left ventricular cavity. Pacing electrodes were sutured to the left atrium and a catheter for recording aortic pressure was introduced via a femoral artery. The dogs were allowed at least 1 week for recovery before administration of the anaesthetics at 2–3-day intervals. Minaxolone and thiopentone were administered to all six dogs, but methohexitone and etomidate to only three.

Minaxolone 2.5 mg kg^{-1} i.v. (which produces about 60 min loss of righting reflex) elicited an immediate and persistent tachycardia (group mean preinjection control value ± SEM 89 ± 7.5 beat min^{-1}; % change 5 min after induction, $\Delta 5' = +64 \pm 10.8\%$, $P < 0.05$, paired *t* test). This was accompanied by immediate and persistent significant reductions in mean aortic pressure (120 ± 7.1 mm Hg; $\Delta 5' = -31 \pm 2.9\%$), systemic vascular resistance (4750 ± 590 dyn $\mathrm{s}^{-1}\ \mathrm{cm}^{-5}$; $\Delta 5' = -38 \pm 4.4\%$) and LV $\mathrm{d}P/\mathrm{d}t_{\max}$ (4180 ± 287 mm Hg s^{-1}; $\Delta 5' = -27 \pm 8.8\%$). Although stroke volume was reduced significantly throughout anaesthesia (2.1 ± 0.18 ml kg^{-1}; $\Delta 5' = -30 \pm 5.1\%$), cardiac output increased immediately on induction, returned to control over 15 min (188 ± 25 ml $\mathrm{kg}^{-1}\ \mathrm{min}^{-1}$; $\Delta 0.5' = +41 \pm 6.7\%$, $\Delta 5' = +13 \pm 8.5\%$) and remained near control value throughout the remaining period of recording. Minaxolone 1.25 mg kg^{-1} produced smaller but qualitatively similar effects.

Thiopentone 24 mg kg^{-1} produced anaesthesia of similar depth and duration to that of minaxolone 2.5 mg kg^{-1} and caused similar haemodynamic effects, although at 5 min after induction arterial pressure and systemic vascular resistance were reduced significantly less than after minaxolone. Thiopentone produced more respiratory depression than minaxolone (apnoea times, thiopentone 32 ± 4.5 s, minaxolone 15 ± 6.7 s), and there was a rebound recovery in aortic pressure, systemic vascular resistance and LV $\mathrm{d}P/\mathrm{d}t_{\max}$ 1–2 min after injection. Ventricular arrhythmias occurred in one dog. Thiopentone 12 mg kg^{-1} produced more tachycardia but less depression of other haemodynamic variables than minaxolone 1.25 mg kg^{-1} but its duration of action was shorter.

Methohexitone 12 mg kg^{-1} elicited a marked tachycardia accompanied by reductions in aortic pressure, systemic vascular resistance and LV $\mathrm{d}P/\mathrm{d}t_{\max}$, which were succeeded by large rebound recoveries 1–2 min after injection. Cardiac output was increased during the period of maximum tachycardia.

Haemodynamic responses to etomidate 4 mg kg^{-1} differed from those occurring after minaxolone or the barbiturates. Heart rate did not vary significantly on induction, but aortic pressure and LV $\mathrm{d}P/\mathrm{d}t_{\max}$ were reduced significantly ($\Delta 5' = -28 \pm 0.6\%$ and $-34 \pm 4.4\%$) and cardiac output decreased during sleep.

When minaxolone 2.5 mg kg^{-1} or thiopentone 24 mg kg^{-1} was given during atrial pacing at about 190 beat min^{-1}, cardiac output remained near normal, indicating that rate changes alone were not responsible for the maintenance of cardiac output.

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THE EFFECTS OF HIGH-DOSE FENTANYL ON RENAL FUNCTION IN THE ANAESTHETIZED DOG

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The effect of fentanyl on renal function, even in high dosage, is usually considered to be small both in the human subject (Gorman and Craythorne, 1966) and in the dog (Bidwai et al., 1976; Hunter et al., 1979).

The effect of low-dosage and high-dosage fentanyl on renal function has been investigated in 10 dogs anaesthetized with nitrous oxide and oxygen, neuromuscular block being provided by alcuronium and ventilation being controlled. In each experiment the animal was initially given fentanyl 0.005 mg kg^{-1} over a 90-min period and estimated renal plasma flow (ERPF: measured by clearance of para-aminohippuric acid), glomerular filtration rate (GFR: measured by clearance of inulin), urine volume ($\dot{V}$), mean arterial pressure (MAP), and renal vascular resistance (RVR) were measured at intervals of 30 min for 90 min. Fentanyl 0.025 mg kg^{-1} was given i.v. over a 10-min period and the variables were measured at intervals of 30 min. A significant reduction in ERPF ($P<0.01$), GFR ($P<0.001$), $\dot{V}$ ($P<0.01$) and MAP ($P<0.001$) occurred together with an increase in RVR ($0.02>P>0.01$); these changes were accompanied by a bradycardia if no atropine was given. The administration of atropine before the high-dose fentanyl prevented bradycardia but did not prevent the alteration in renal function.

The effect of high-dose fentanyl on renal function appeared to be of relatively short duration. Within 90 min the measurements had returned to the values found with low-dose fentanyl.

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MONITORING RESPIRATORY FUNCTION WITH A MICROCOMPUTER

G. N. C. Kenny, P. D. Davis and D. Campbell
University Department of Anaesthesia, Glasgow Royal Infirmary

The value of the analysis of volume–pressure relationships in monitoring pulmonary function has been reported by several workers (Peters, Hilberman and Hogan, 1972; Proctor and Woolson, 1973; Hilberman et al., 1975). The advantages of such analyses include the detection of malfunction of the ventilator, the detection of pneumothorax and, from the calculation of respiratory work, the provision of a reliable index of the need for continued ventilator support.

A program and interface have been developed for use with the Commodore PET 2001/8 microcomputer to allow data obtained from a Siemens Servo 900B ventilator to be processed. The interface is based on an integrated circuit which consists of an analog to digital converter combined with a 16-channel multiplexer. The ventilator has analog outputs for pressure, inspiratory flow and expiratory flow. Two channels of the multiplexer are used to obtain the inspiratory flow and pressure. The changeover to expiration is detected and the expiratory values obtained.

The accuracy and linearity of the system in measuring pressure were determined by comparing the pressure displayed by the computer with a water manometer at eight values of pressure from 5 cm H_2O to 40 cm H_2O in increments of approximately 5 cm H_2O pressure. Five separate measurements were made at each pressure.

The accuracy of measurement of the inspiratory flow was determined by passing the gas flow from the inspiratory port of the ventilator through a Parkinson Cowan gas meter over a period of 5 min. The average minute volume obtained was compared with the value calculated by the computer over the same period. Five measurements were made at each of eight minute volumes from a ventilator setting of 2.5 litre min^{-1} to 20 litre min^{-1} in increments of 2.5 litre min^{-1}. The expiratory flow was compared in a similar manner by passing the gas flow from the expiratory port of the ventilator through the gas meter. Five measurements were made on the expiratory flow using the same ventilator settings as for the inspiratory measurements.

The system proved to be accurate and linear for pressure and flows over the ranges measured. The results of the comparison of the computed values with the measured values were:

Pressure: $y = x+0.19$; $r = 0.9999$; SEM of estimate = 0.193.

Inspiratory flow: $y = x$; $r = 0.9993$; SEM of estimate = 0.188.

Expiratory flow: $y = 0.94\,x+0.31$; $r = 0.9997$; SEM of estimate = 0.124.

To obtain such information using manual planimetry would be time-consuming on anything other than a small sample number of traces. An analog system which could produce an equivalent amount of information would be both complex and expensive. The introduction of cheap microprocessor-based computers allows such monitoring to be undertaken even in small intensive care units where resources are at a premium.

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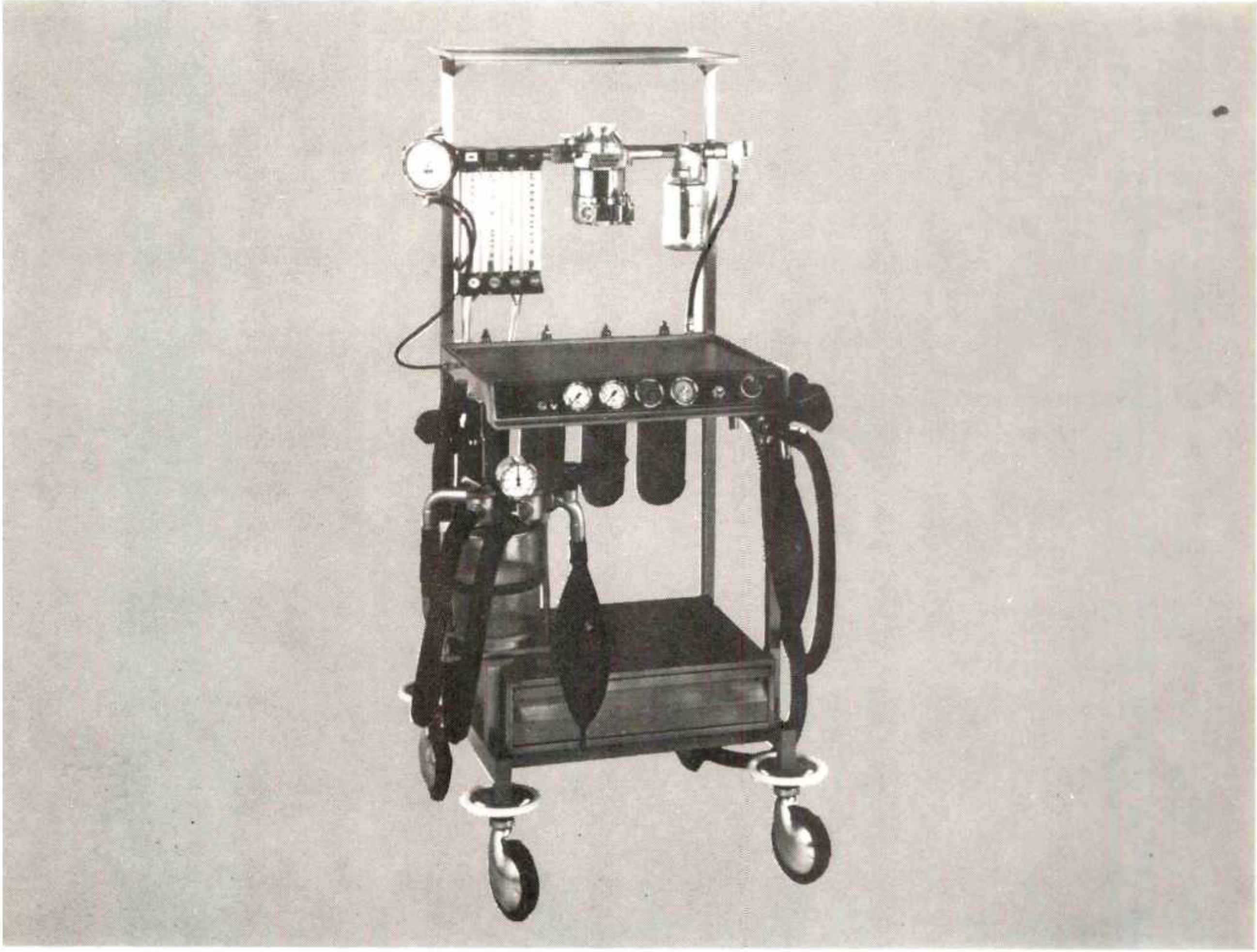

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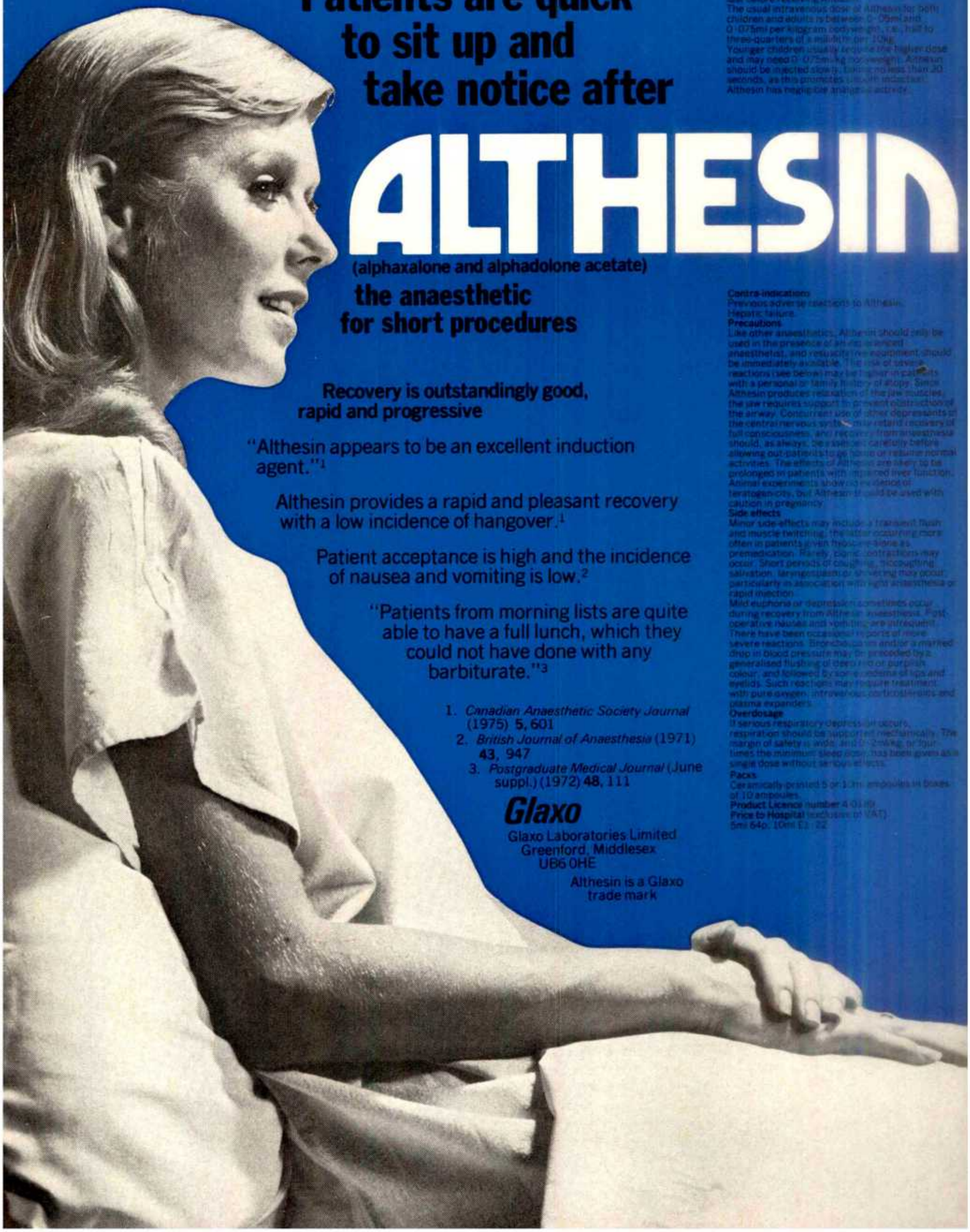

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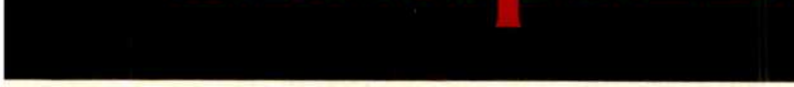

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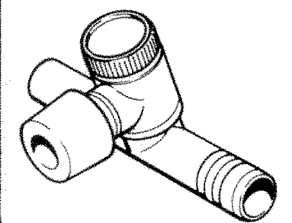

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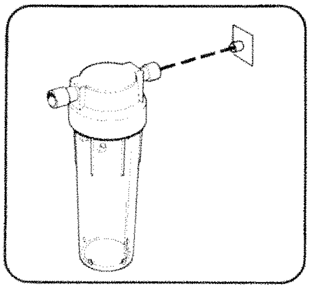

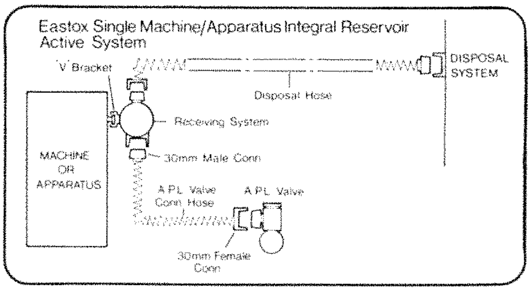

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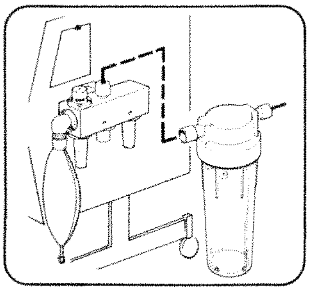

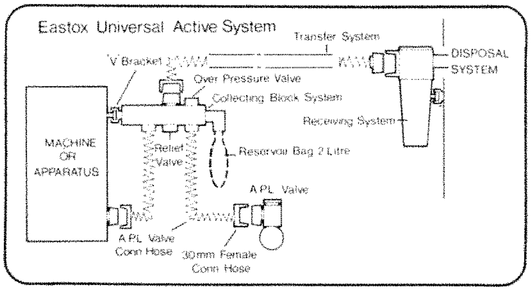

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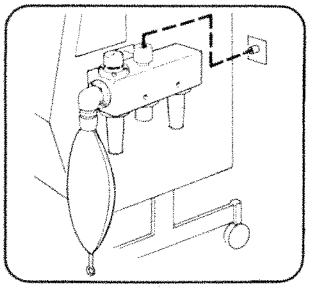

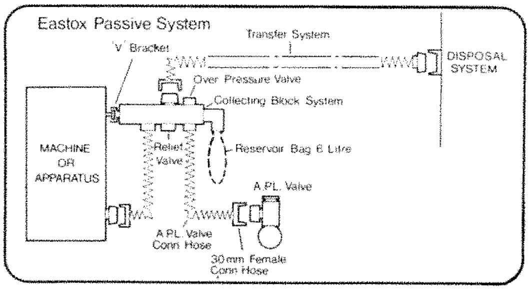

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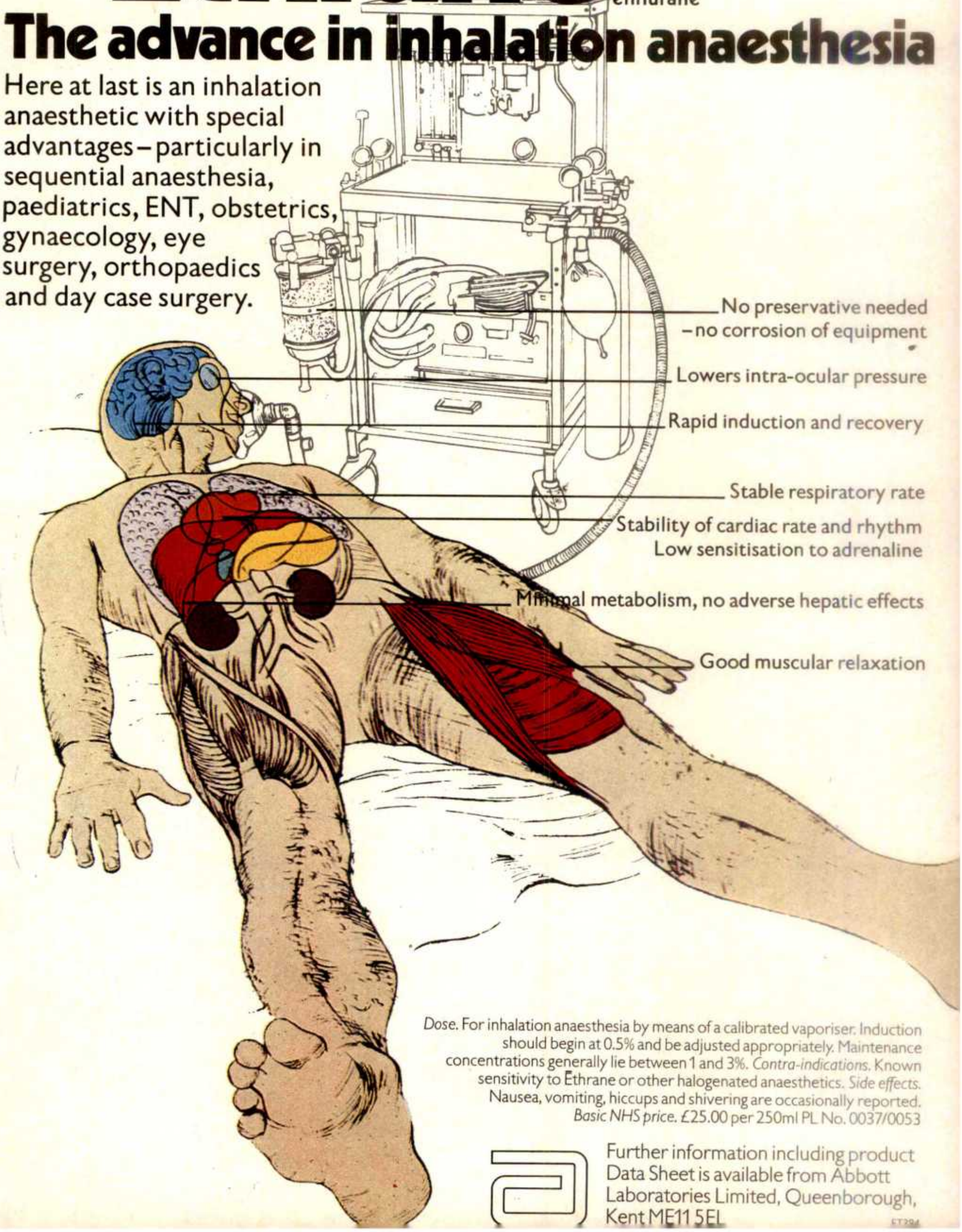
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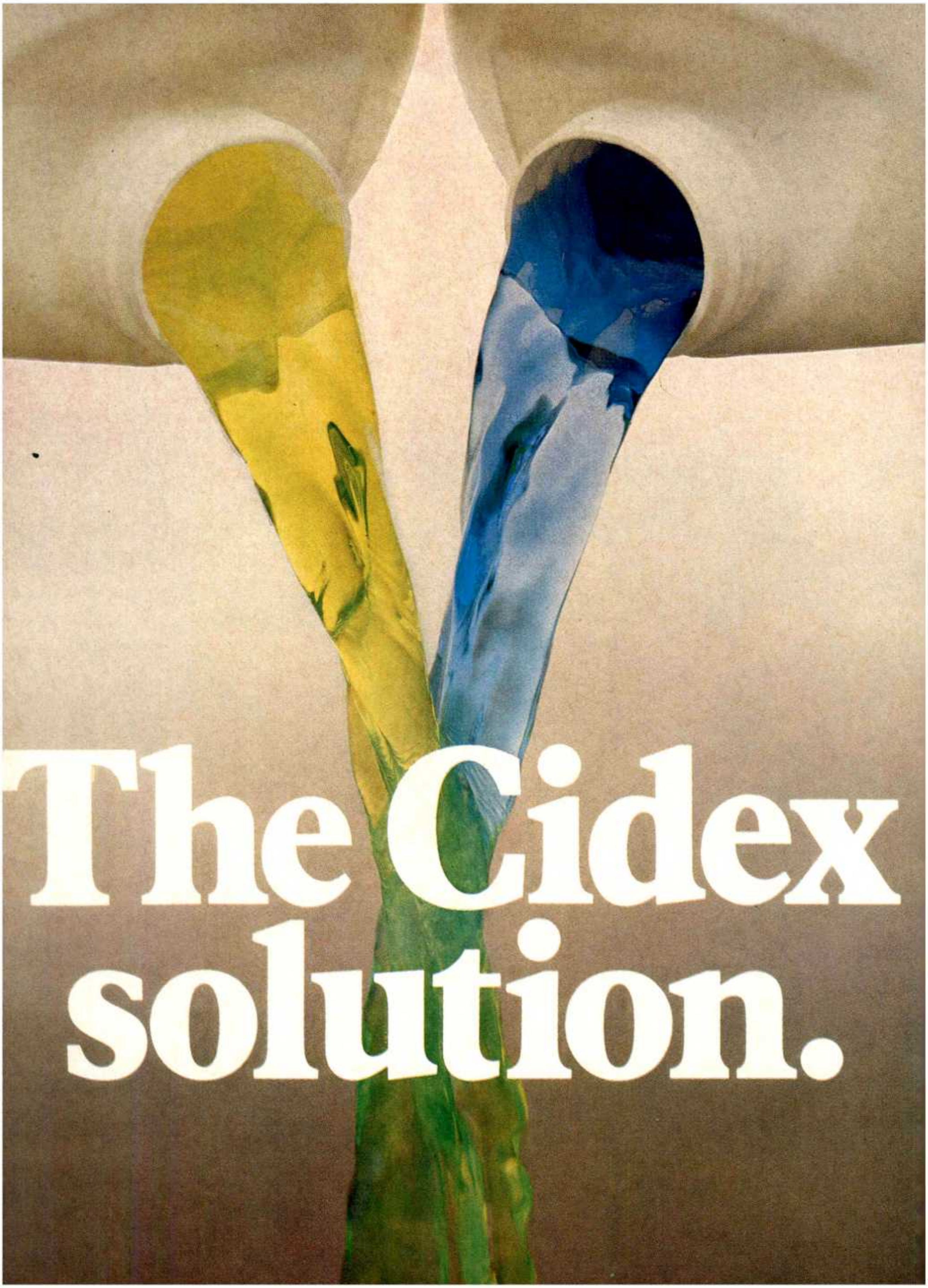
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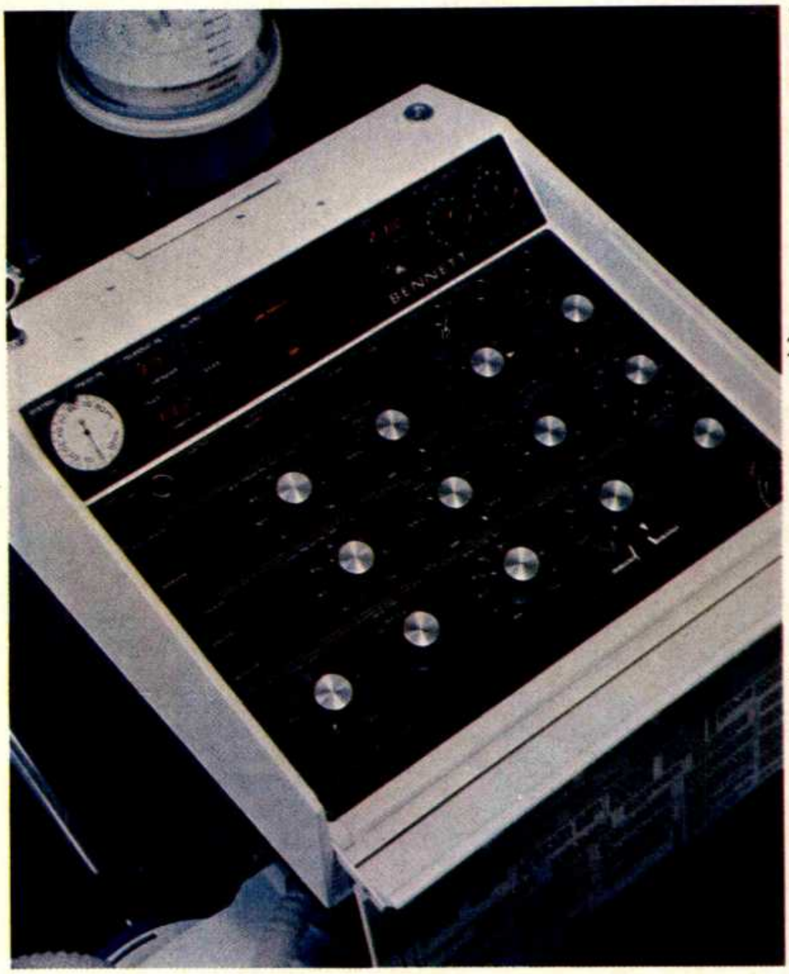

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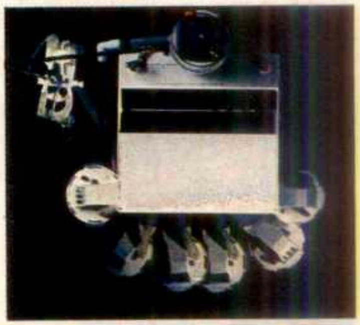

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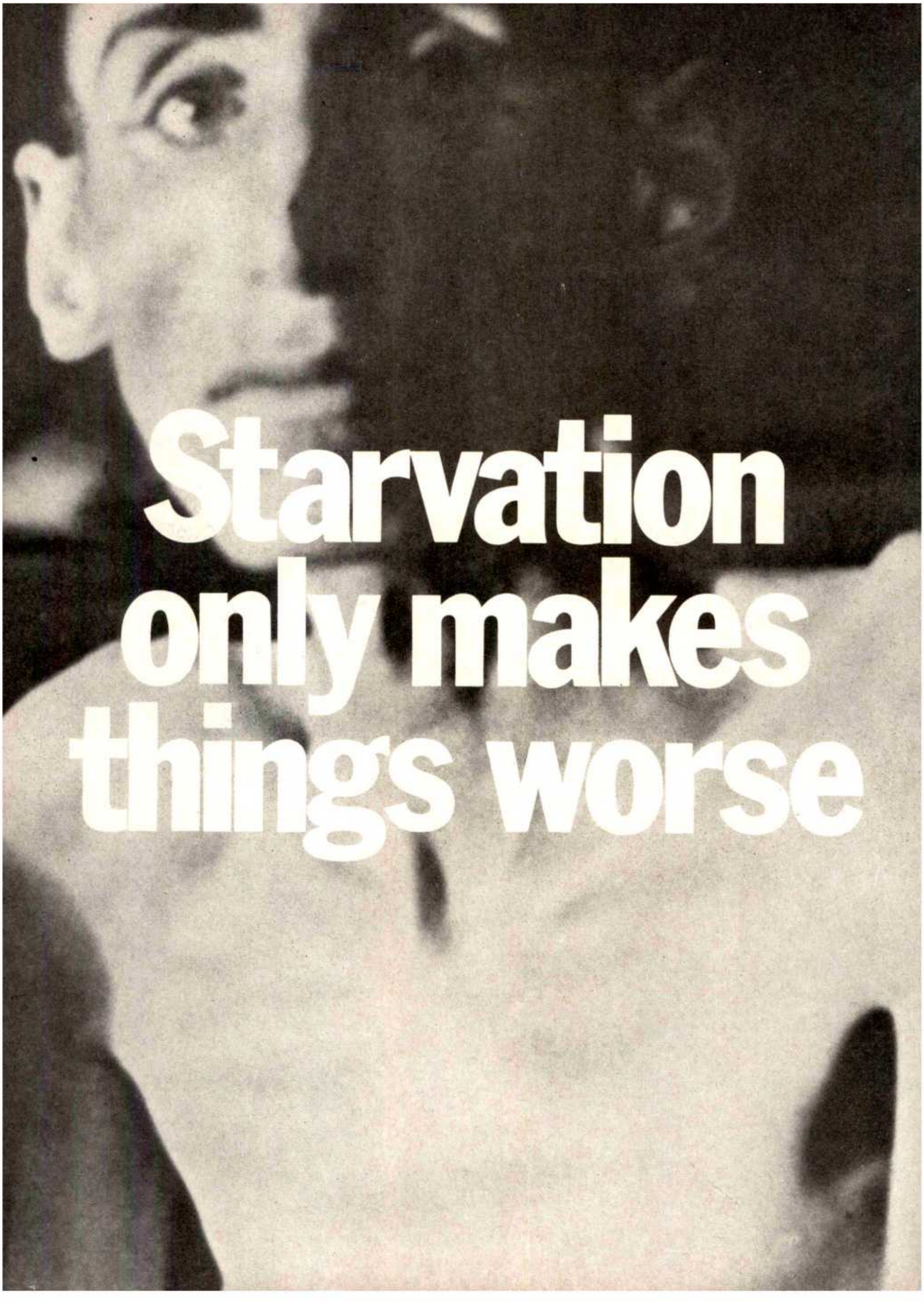
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As with all hypertonic solutions, vein irritation may occur. Do not administer unless the solution is clear and container is undamaged.

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Synthamin 9 without electrolytes (PL 0116/0067) 500ml £5.65.
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Synthamin 17 (PL 0116/0056) 500ml £9.80.
Synthamin 17 without electrolytes (PL 0116/0069) 500ml £9.45.

References

1. Daly, J.M., Vars, H.M., and Dudrick, S.J. (1972). Effects of protein depletion on strength of colonic anastomoses. Surgery Gynec. Obstet., *134*, 15-21.
2. Alexander, J.W. (1974). Emerging concepts in the control of surgical infections. Surgery, *75*, 934-946.
3. Silk, D.B.A. (1978). Clinical nutrition in hospital – 1. Principles. Hospital Update, *4*, 483-489.

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Two copies of each manuscript should be submitted and should indicate the title of the paper, the name(s), qualifications and full addresses) of the author(s), and be in double-spaced typing on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss.

Papers in recent issues of the *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables
Illustrations

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There should be a separate title page, including the name(s), degrees and address(es) of author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

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The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

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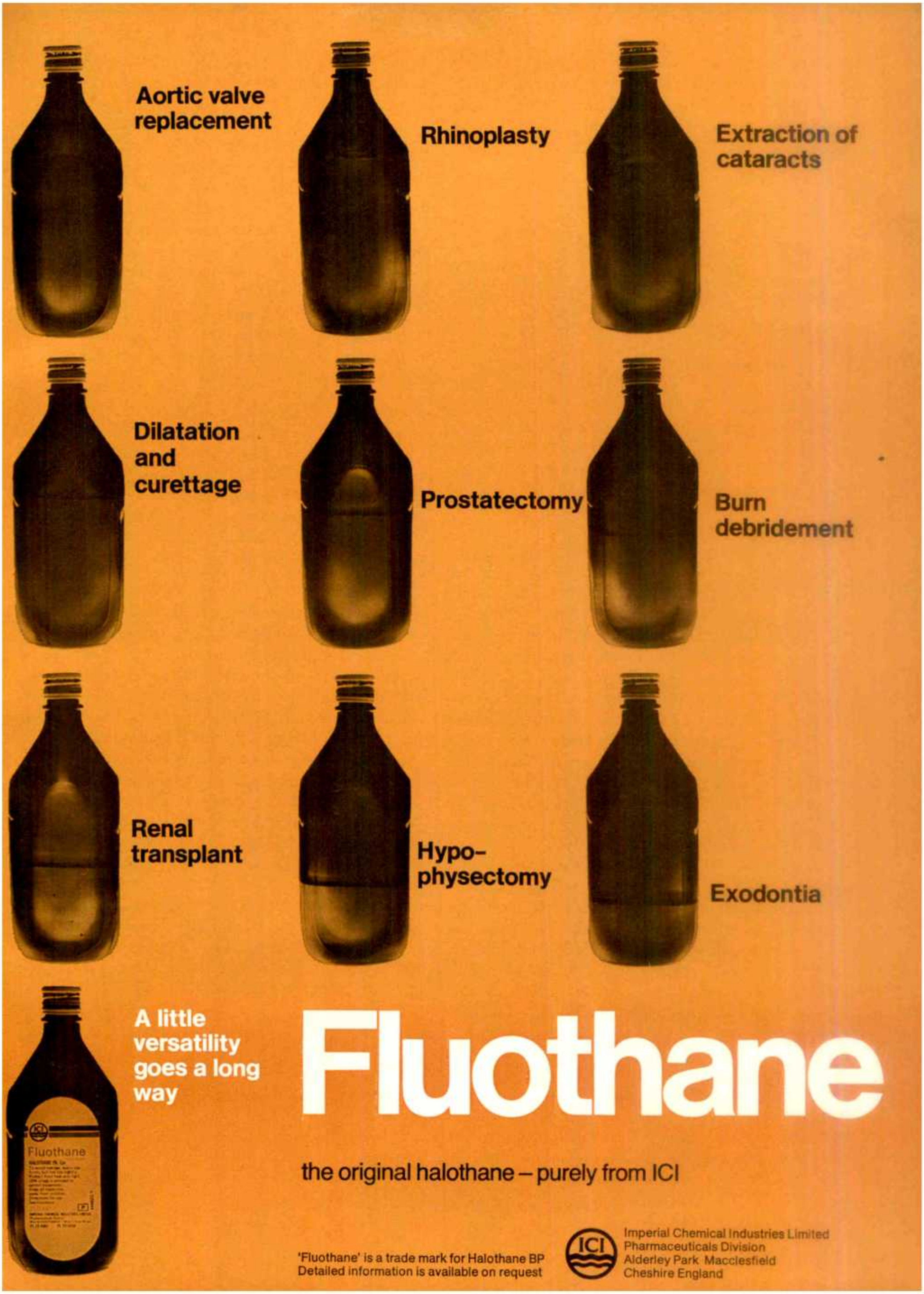

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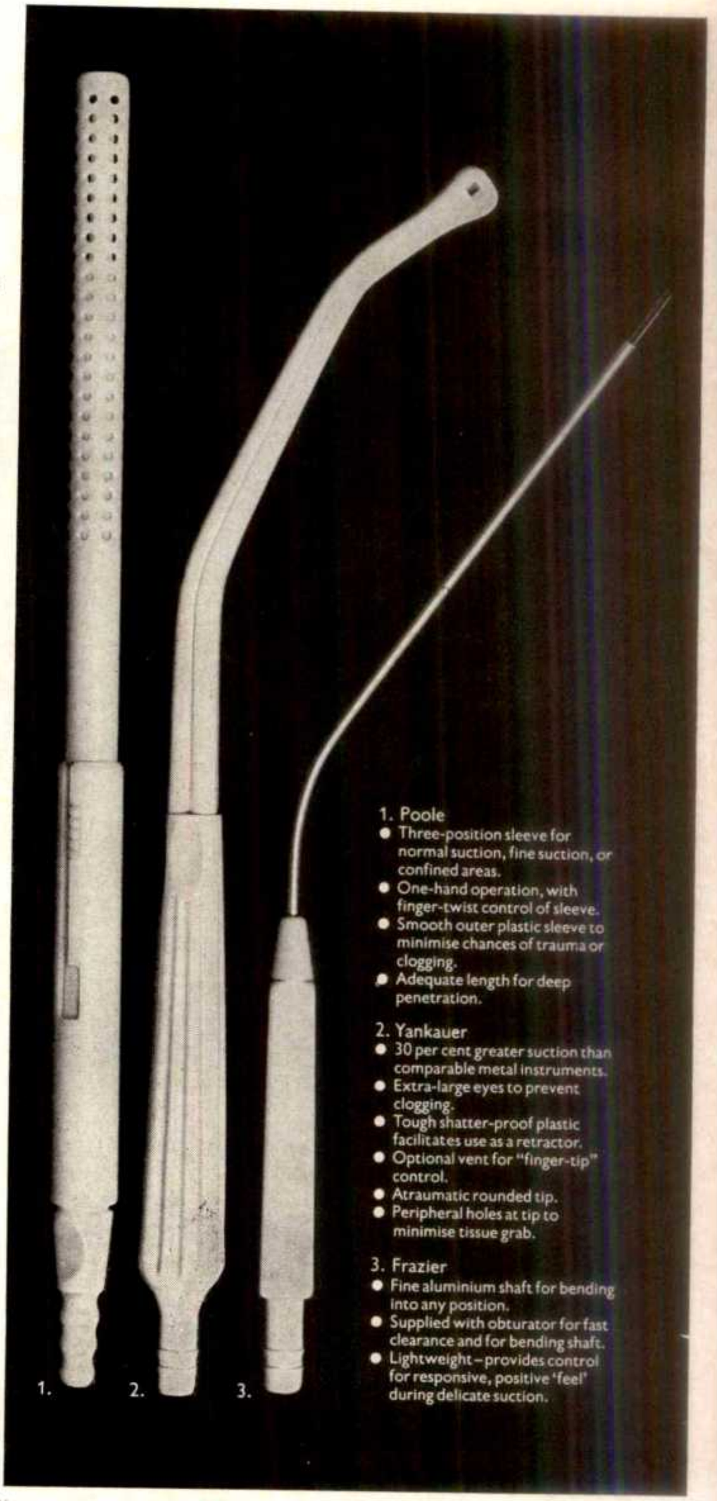

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Legal category No legal restrictions on sale or supply.

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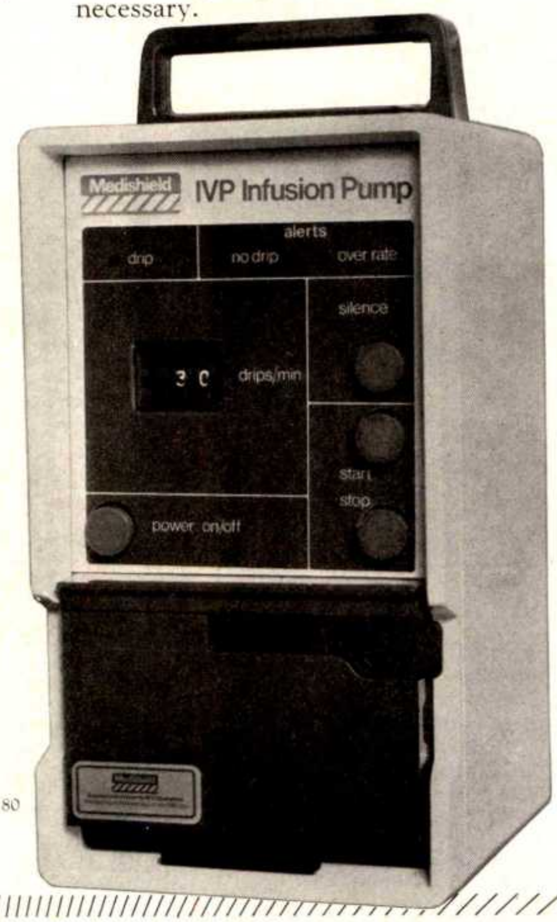

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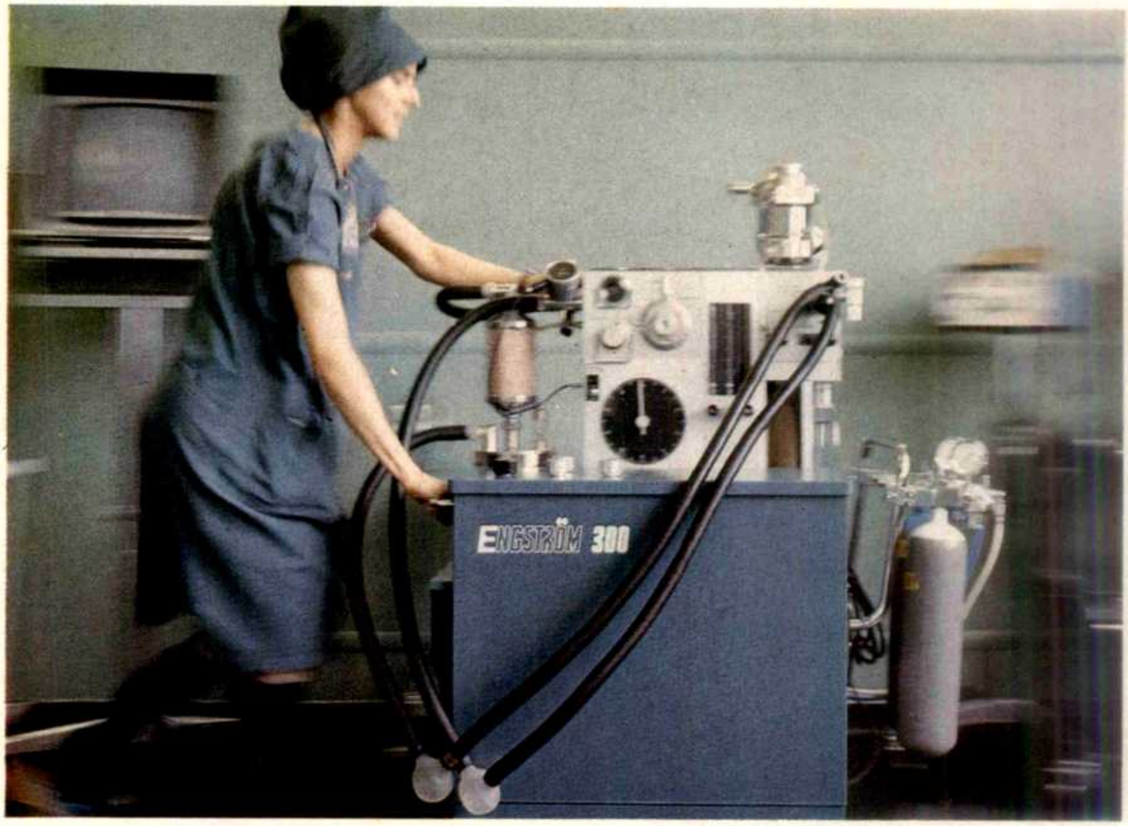

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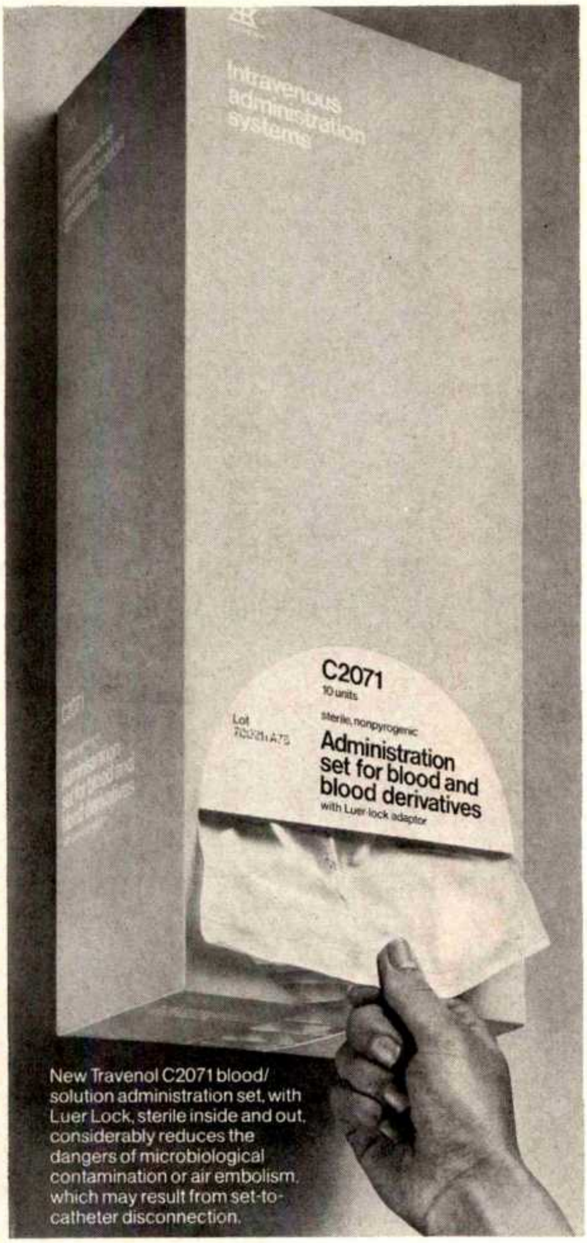
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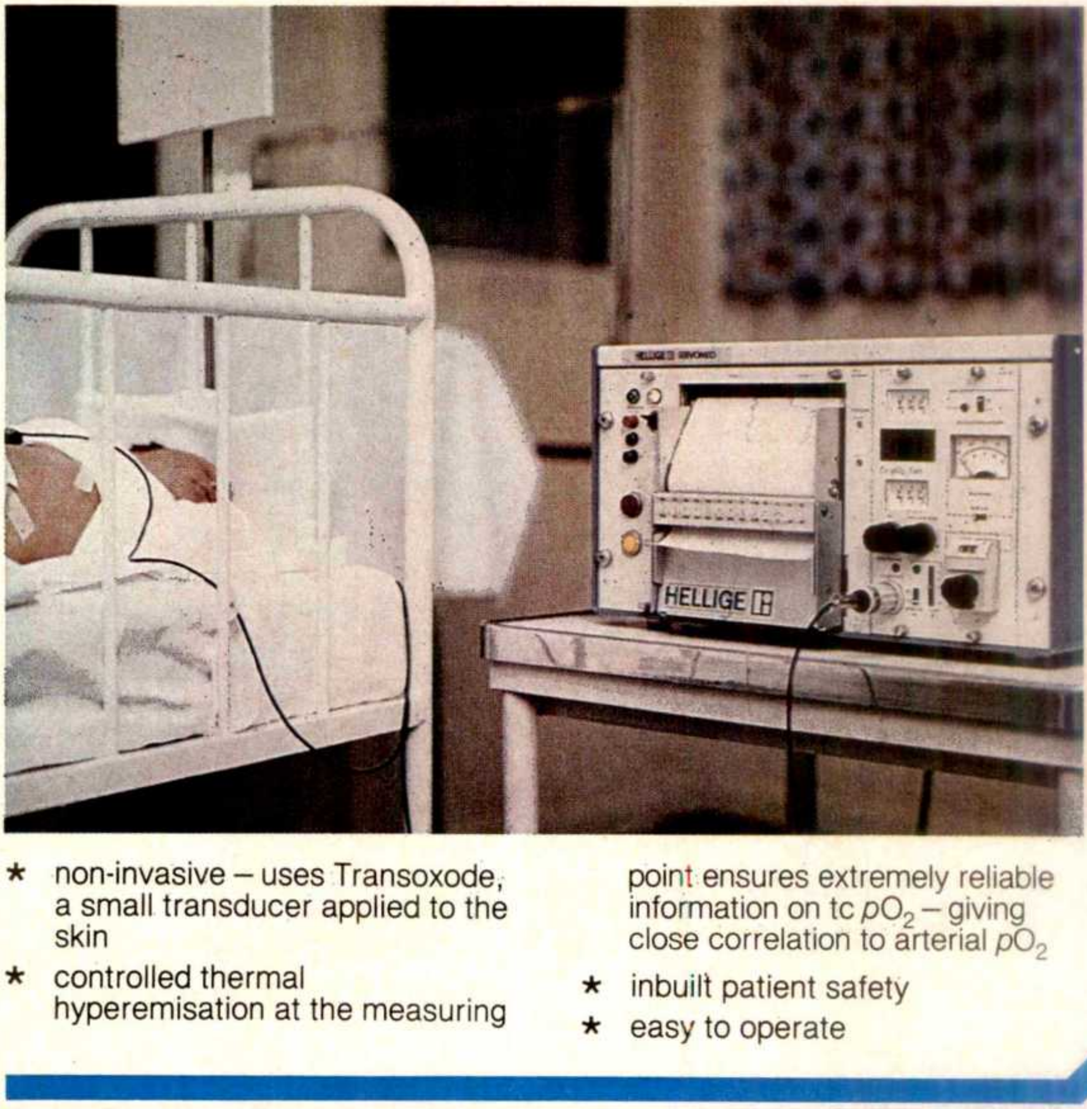

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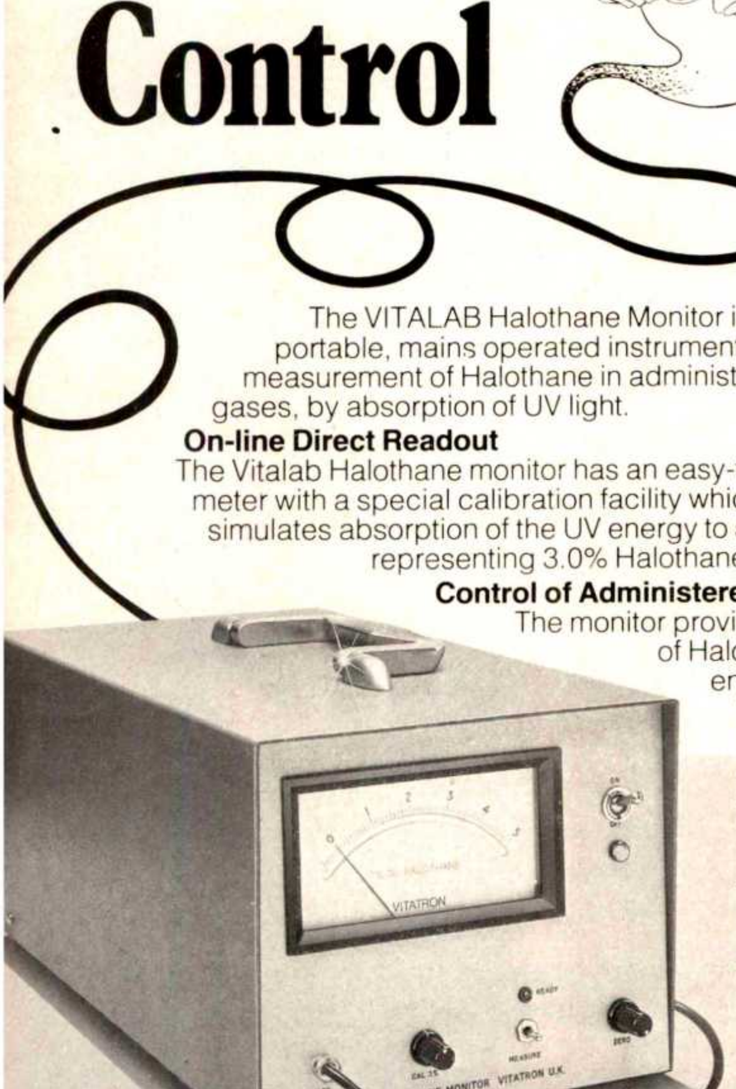

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1) Schneider et al., Chirurg **47,** 185 (1976)
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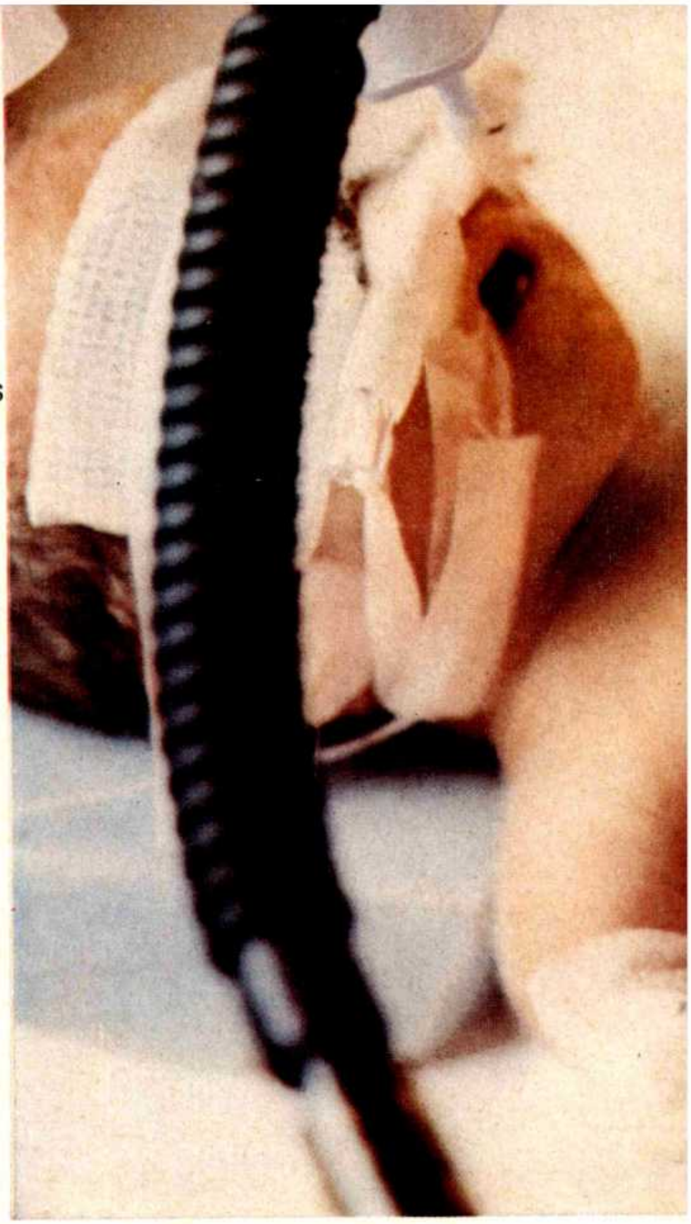

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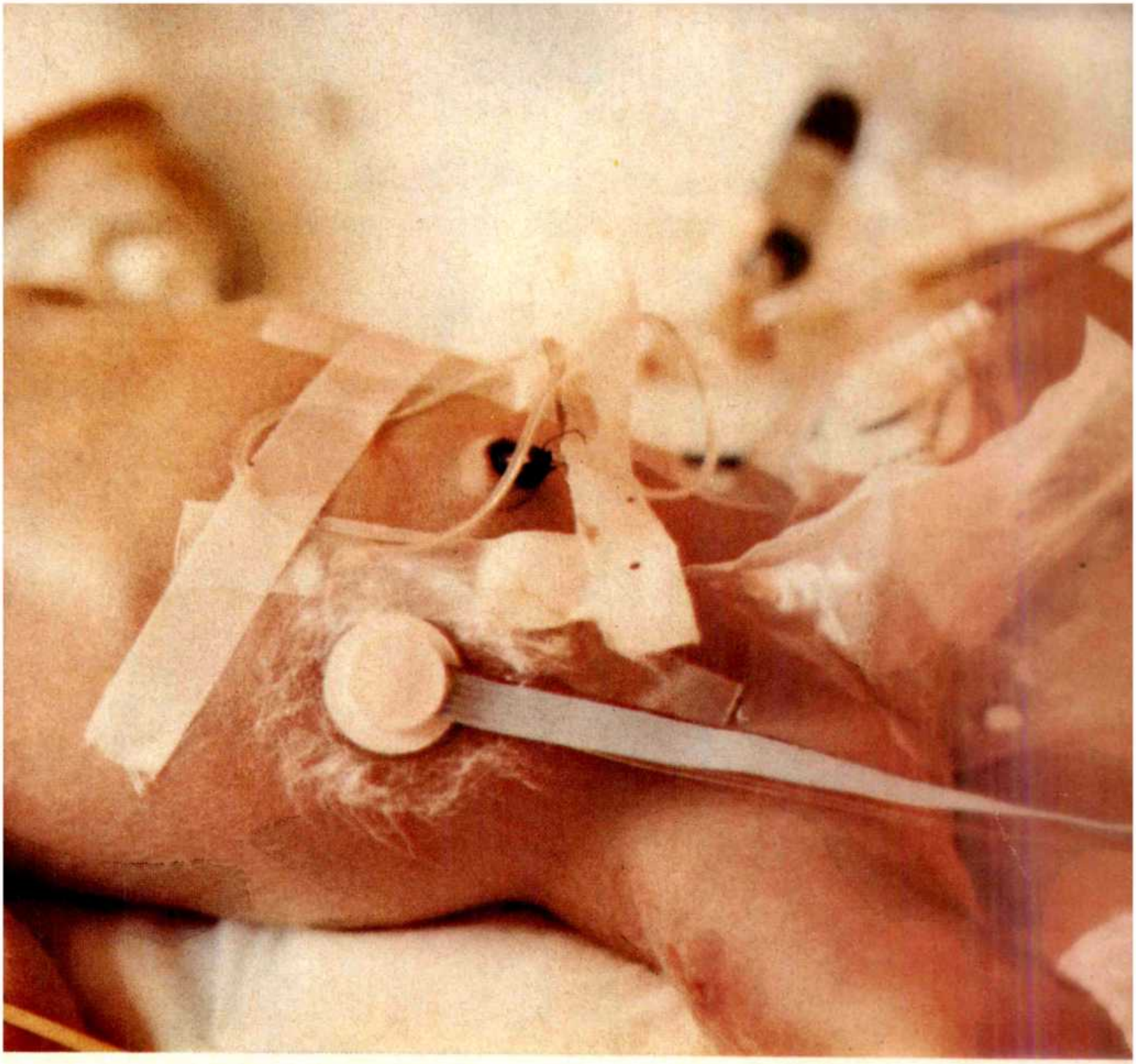

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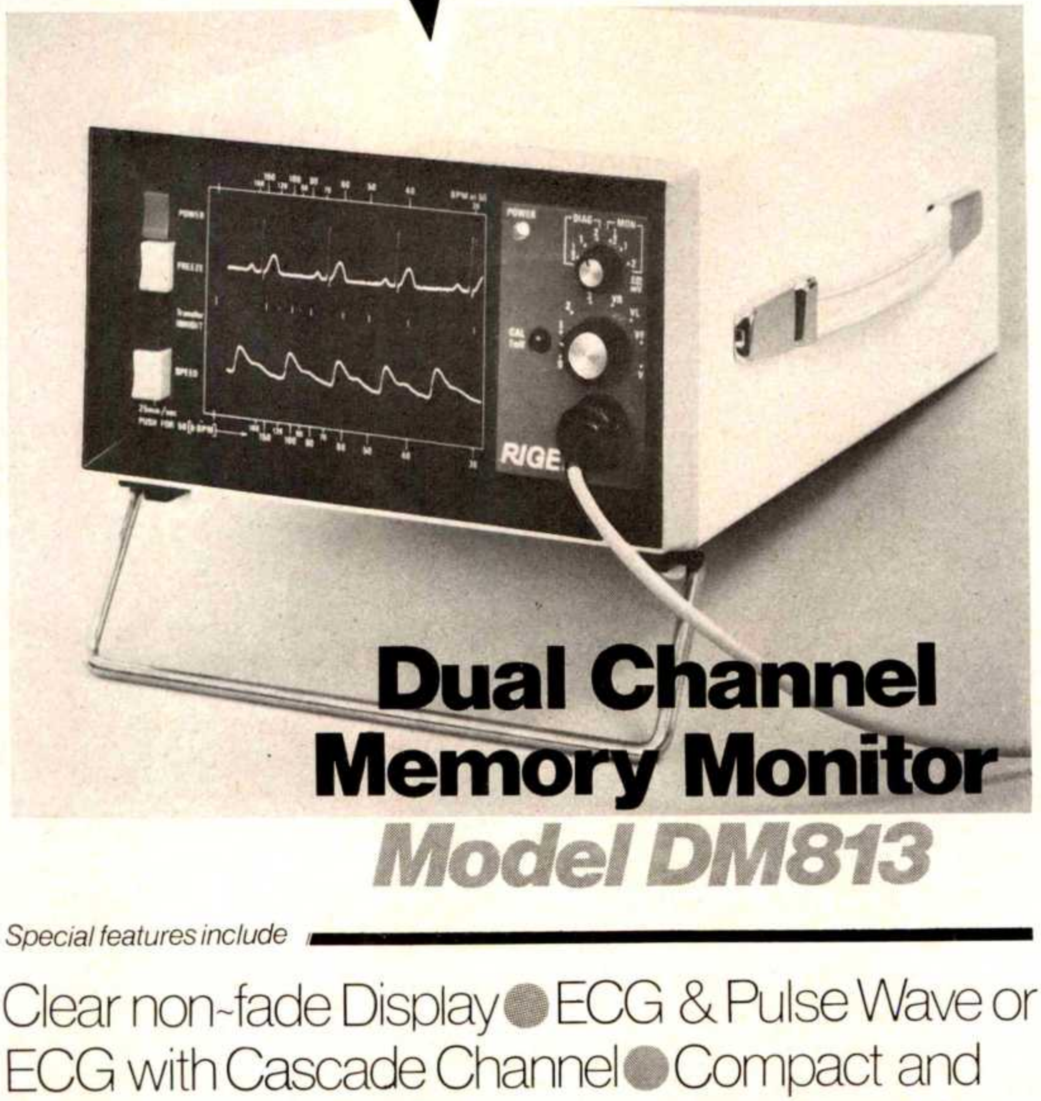

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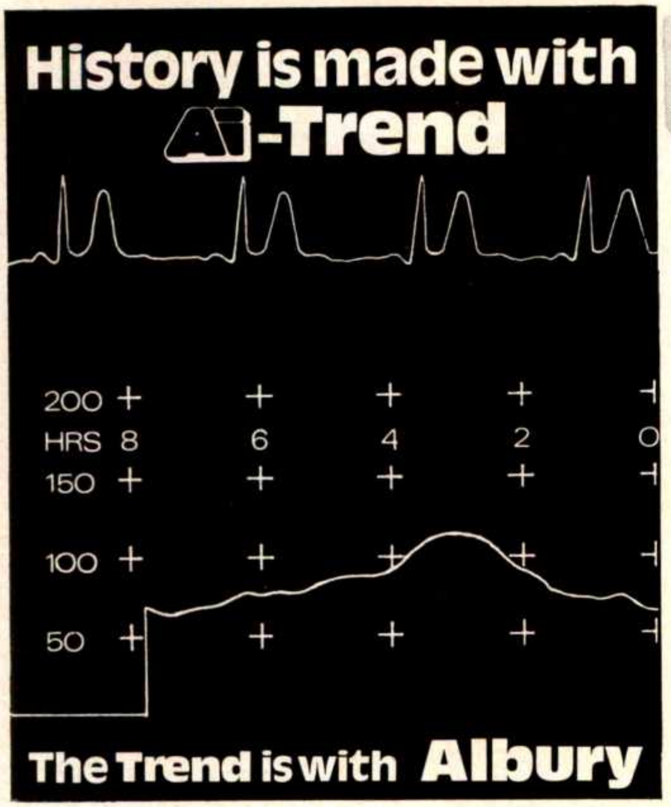

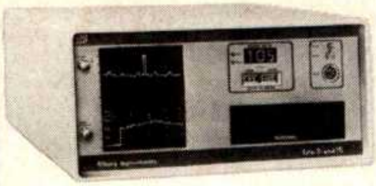

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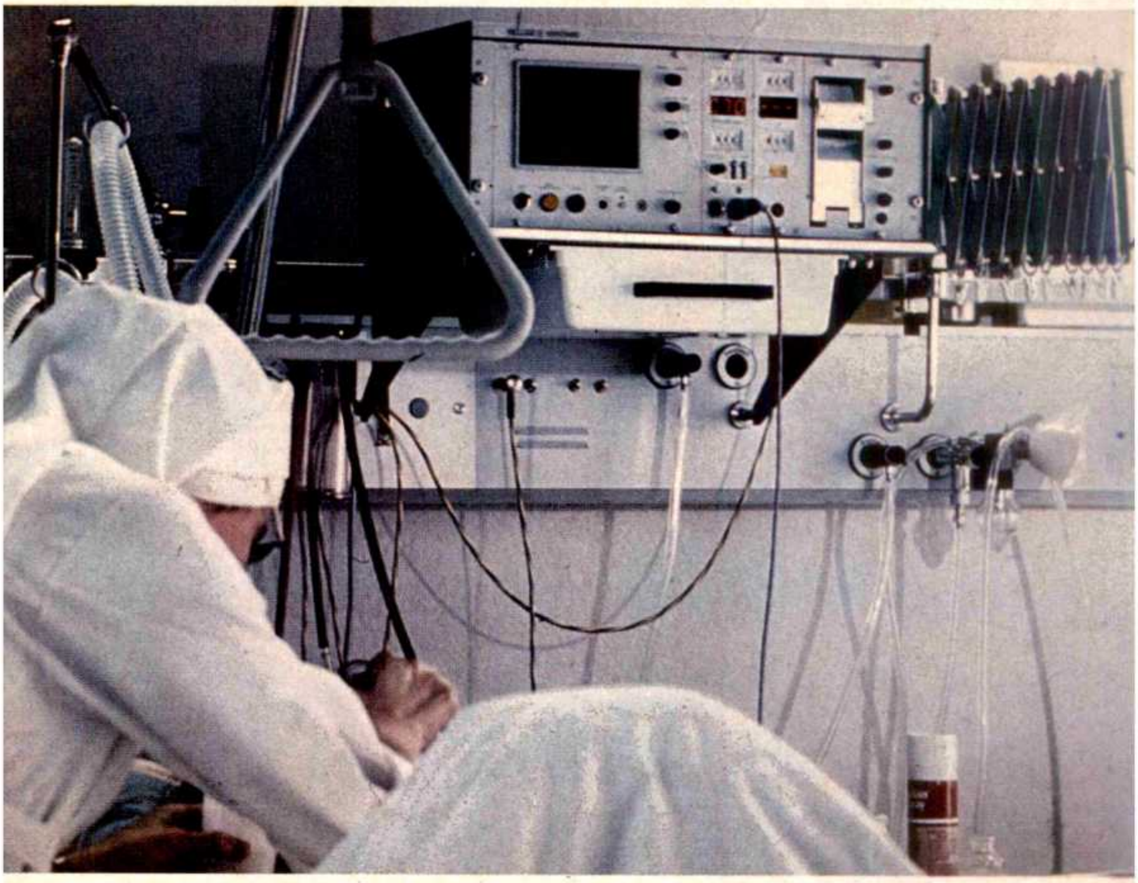

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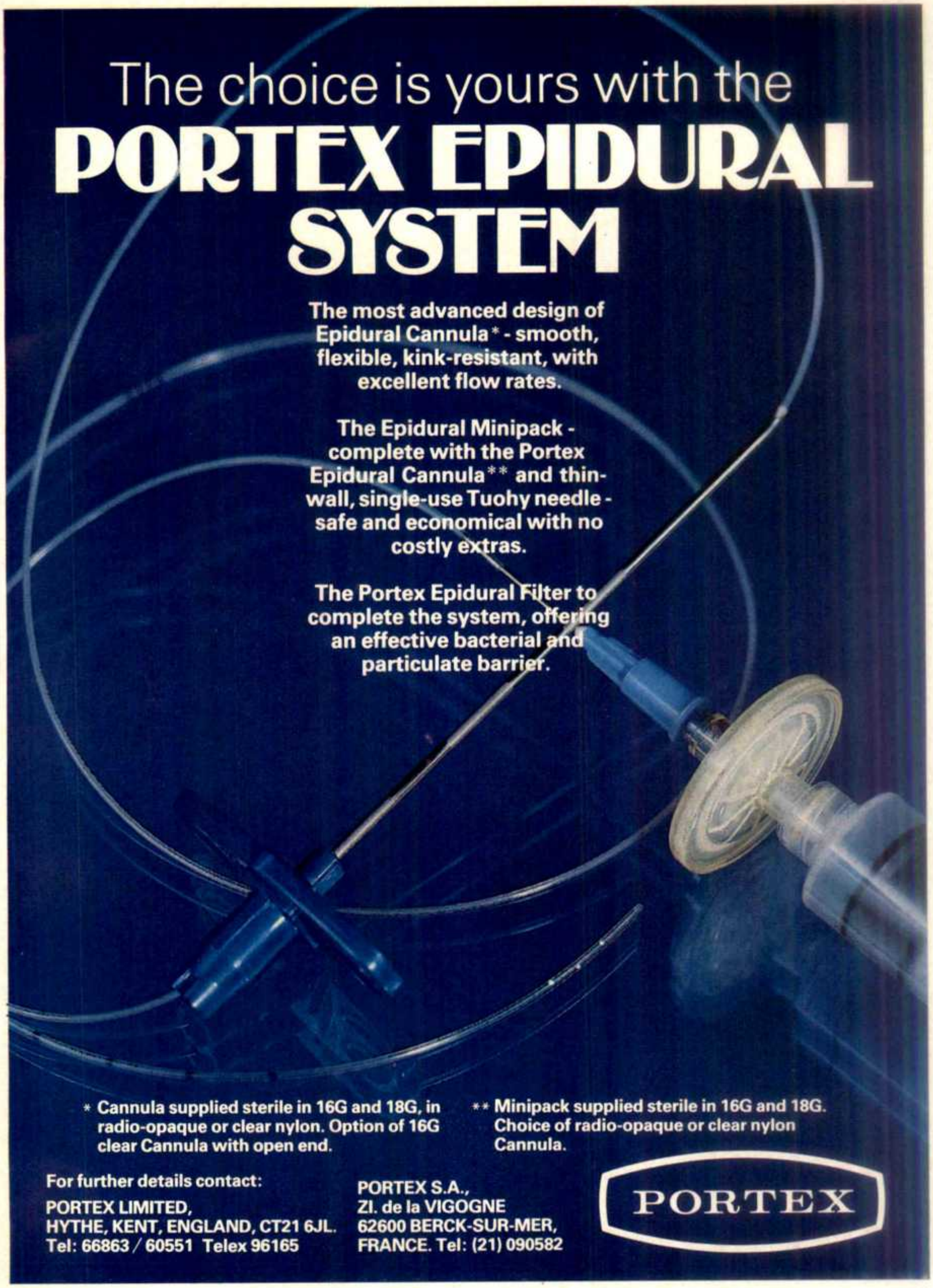

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John S. McDonald, M.D.,
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London WC1H 9LG.

MANCHESTER MEDICAL SOCIETY

Programme 1979–80

November 8	Professor J. P. Payne (R.C.S.E.): "The assessment of neuromuscular activity in anaesthetized man".
December 13	Presidential Address, Dr R. I. Keen: "Anaesthesia—A dangerous specialty?"
January 10	Dr Brian Kay: "Recent advances in narcotic analgesic anaesthesia".
February 14	Registrars' Papers.
March 20	Symposium: "Aspects of anaesthesia and trauma".
April 17	Joint meeting with the Liverpool Society of Anaesthetists. Dr David Scott, Dr Y. Y. Youssef.

All meetings at 8.15 p.m. at the University of Manchester Medical School, except the meeting on March 20, which will be at 8.15 p.m. at the Bolton Medical Institute.

NORTH EAST OF SCOTLAND SOCIETY OF ANAESTHETISTS

Programme 1979–80

November 8	Dundee. Dr Richard Ellis (Leeds): Malignant Hyperthermia.
March 13	Stracathro. Registrars' Papers.
April 10	Aberdeen. Dr Peter Baskett (Association of Anaesthetists): The Separate College.
May 15	Stracathro. Annual General Meeting and Presidential Address.

Meetings are held at 8.00 p.m. in Aberdeen Royal Infirmary, Ninewells Hospital and in Stracathro Hospital, Brechin, unless otherwise notified.

Honorary Secretary:

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Telephone: 681818, extn 2021

GLASGOW AND WEST OF SCOTLAND SOCIETY OF ANAESTHETISTS

Programme 1979–80

November 20	Dr A. F. Lever (M.R.C. Blood Pressure Unit, Western Infirmary).
January 23	Members' Night: presented by members of Division of Anaesthesia, Western Infirmary.
February 14	Dr J. C. Stoddart (Royal Victoria Infirmary, Newcastle-Upon-Tyne): "The Rational Use of Intensive Therapy".
March 18	Presidential Address: Dr D. D. Moir.
April 17	Annual General Meeting.
May 22	Golf Outing, Williamwood Golf Club, 2 p.m.

Meetings will take place in the Royal College of Physicians and Surgeons of Glasgow, 242 St Vincent Street, Glasgow.

Honorary Secretary:

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Glasgow G11 6NT.
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THE NORTHERN IRELAND SOCIETY OF ANAESTHETISTS

Programme 1979–80

November 28	Dr G. H. Bush (Alder Hey Children's Hospital, Liverpool): "Upper Airway Obstruction in Children".
January 9	Dr J. Moore and Dr J. Howe (Department of Anaesthetics, Queen's University Belfast): "Cimetidine in Obstetrics".
February 13	McKee Room, Belfast City Hospital. Prof. D. G. McDowall (Department of Anaesthetics, University of Leeds): "A Regime of Head Injury Management".
February 29	Dining Club, Royal Victoria Hospital. Annual Dinner.
March 12	McKee Room, Belfast City Hospital. Prof. W. W. Mapleson (Department of Anaesthetics, Welsh National School of Medicine, Cardiff): "Physical Principals of Paediatric Anaesthetic Equipment".
April 2	Annual General Meeting.

Meetings take place in the Sir Samuel Irwin Lecture Theatre, Royal Victoria Hospital, unless otherwise stated, and commence at 6.30 p.m. They will be followed by a Buffet Supper.

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Der *Anaesthesist*

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VOLUME 15, No. 11 NOVEMBER 1979

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EDITORIAL

RESEARCH IN THE EIGHTIES

"Lest we forget" is the title of two recent meetings of the Anaesthetic Section of the Royal Society of Medicine at which retired senior anaesthetists related their pioneering work in the development of clinical anaesthesia. These speakers recalled events such as the introduction of tracheal intubation, early days of thoracic anaesthesia, the use of hypothermia and the clinical application of myoneural blocking drugs. They highlighted the part British anaesthetists played in the development of our specialty in the later 1930's and in the 1940's.

It is interesting to note that none of these anaesthetists would, by today's standards, be called a "research worker". Perhaps none of their early papers would now be acceptable at a scientific meeting. Editors might return their manuscripts because of lack of statistical data or a predominance of clinical impressions rather than scientific facts.

Today we have many academic departments, most of which have a number of staff engaged in research. Some of these people have had a training in basic sciences and use their knowledge of physiology, pharmacology, electronics and physics. Sophisticated monitoring equipment is available, computerized records simplify data storage and retrieval, and autoanalysis quickly provides the required biochemical information.

It is not likely that any of today's professors of anaesthesia will make the same impact on our specialty as did Magill or Macintosh. They were anaesthetists with an enquiring mind who sought an answer to their clinical problems and, having found it, made the knowledge available to their colleagues. Similarly, none of today's writers is likely to make as much impact as did Hewer and Lee.

We can look at the 1970's as a decade of consolidation of knowledge of anaesthetic agents and adjuvants and of the physiological changes produced by various techniques. We have looked for better inhalation and i.v. agents, myoneural blocking drugs and analgesics. A variety of forms of neuroleptanalgesia have developed from the lytic cocktail, and spinal and extradural techniques have been re-evaluated. Worthwhile research has been carried out on the mode of action of drugs and on their long-term toxic effects.

Anaesthesia can now be more pleasant for the patient that it was a decade ago. Moreover, the routine work of many anaesthetists has become more interesting in this decade.

While we may not make the advances of the pioneers referred to above, there is still plenty of scope for research. However, research workers need a feed-back from practising anaesthetists. Their limited clinical exposure makes it unlikely that they themselves will come across clinical problems which require investigation. Prolonged suxamethonium apnoea, tissue damage after arterial injection of thiopentone, jaundice after repeat anaesthesia and hypersensitivity to Althesin are only a few of the pharmacological problems which were first noted by practising anaesthetists. A record sheet, clip board and pen or pencil are readily available to every anaesthetist and were the main tools of some of the pioneers of our specialty. Good clinical notes can reveal a lot of useful information and show the research worker the field to which he should direct his efforts. Many of the new drugs, anaesthetic machines and ventilators evaluated in the seventies were the brainchild of the pharmaceutical or equipment industries. Let the clinicians document the failings of our available agents or machines and the companies will know wherein lies the most profitable field for research. Proper feed-back from clinicians to research workers and industry will make research relevant to all concerned.

John W. Dundee

Br. J. Anaesth. (1979), **51**, 999

CONTINUOUS MEASUREMENT OF BLOOD GASES *IN VIVO* BY MASS SPECTROMETRY

P. Foëx, G. Burt, P. Maynard, W. A. Ryder and C. E. W. Hahn

SUMMARY

Continuous analysis of oxygen and carbon dioxide tension in the blood phase, over periods of 4–5 h, was carried out in the pulmonary artery (93 determinations in six anaesthetized dogs) and in the aorta (29 determinations in four anaesthetized dogs). Silastic-covered stainless steel catheters attached to a mass spectrometer were used. The mass spectrometer signals were linearly related to the blood-gas tensions measured by conventional analysis. The mass spectrometer signals were calibrated *in vivo* by exposing the animals to high and low oxygen and carbon dioxide tension. With such *in vivo* calibration the slopes of the straight line regressions for mass spectrometer $P\text{O}_2$ or $P\text{CO}_2$ on $P\text{O}_2$ or $P\text{CO}_2$ by conventional analysis were comprised between 0.944 and 1.031 while the standard error of the slopes were between 0.019 and 0.031. Deliberate reductions of cardiac output had little effect on the mass spectrometer readings.

The mass spectrometer is commonly used for continuous analysis of concentrations of respiratory gases. Hunter, Stacey and Hitchcock (1949) made an instrument with three fixed collectors aligned to receive nitrogen, oxygen and carbon dioxide simultaneously, thus opening the way to breath-by-breath multivariate analysis of respiratory gases. Many applications of the respiratory mass spectrometer have been reviewed by Fowler (1969).

In 1966 Woldring, Owens and Woolford used a mass spectrometer to measure $P\text{O}_2$ and $P\text{CO}_2$ in the aorta of the cat. Hass, Siew and Yee (1968) used a mass spectrometer to measure nitrogen and nitrous oxide concentrations in man with a view to measuring cerebral blood flow. Since then a number of articles have dealt with measurement of gas tensions in the blood phase (Brantigan et al., 1970; Dardik, Dardik and Laufman, 1970; Wald et al., 1970; Brantigan, Gott and Martz, 1972; Roberts et al., 1972; Roberts, Vilinskas and Owens, 1972; Seylaz et al., 1973; Loisance and Owens, 1974; Key, 1975; Brantigan, Dunn and Albo, 1976; Lundsgaard, Groenlund and Einer-Jensen, 1978; Pinard, Seylaz and Mamo, 1978). In most of these articles, new catheters and new types of diffusion membranes have been described and their properties evaluated *in vitro* or *in vivo*, mostly in experimental animals. Similarly, a number of articles have dealt with the application of mass spectrometery to measurement of gas tensions in various tissues (Owens, Belmusto and Woldring, 1969; Dardik, Dardik and Laufman, 1970; Brantigan, Gott and Martz, 1972; Roberts and Owens, 1972; Loisance and Owens, 1974; Wilson and MacGregor, 1976; O'Riordan et al., 1977; Seylaz and Pinard, 1978). Again, most of the published work is concerned with the validation of new catheters and the technique does not appear to have been extensively utilized for physiological studies.

Transcutaneous measurements of blood-gases using a mass spectrometer have been reported (McIlroy, Simbruner, Sonoda, 1978; Parker, Delpy and Reynolds, 1978) and constitute a natural development of the applications of the mass spectrometer for continuous non-invasive determinations of blood-gas tensions.

This preliminary study was undertaken to evaluate the performance, *in vivo*, of a commercially available mass spectrometer (Centronic MGA 200) with its blood mode attachment, including silastic-covered stainless steel catheters (Searle, Scientific Research Instrument Corp.). The experimental design was kept as simple as possible so that conclusions could be drawn on the prospective use of a mass spectrometer for continuous *in vivo* analysis of blood-gas tensions during physiological studies by a group of workers not primarily involved in mass spectrometry.

METHODS

Studies were carried out in 10 dogs. After induction of anaesthesia with thiopentone 15 mg kg^{-1} and

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P. Foëx, M.A., D.PHIL., D.M.; G. Burt, M.B., B.S., F.F.A.R.C.S.; P. Maynard; W. A. Ryder; C. E. W. Hahn, M.SC., D.PHIL.; Nuffield Department of Anaesthetics, University of Oxford.

Correspondence to: P. F., Nuffield Department of Anaesthetics, The Radcliffe Infirmary, Oxford OX2 6HE.

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tracheal intubation, anaesthesia was maintained with 0.8% halothane in a gas mixture containing oxygen, nitrogen and carbon dioxide. Intermittent positive pressure ventilation was applied at constant tidal volume (40 ml kg^{-1}) and rate (12 b.p.m.) using a Penlon–Oxford ventilator. An infra-red carbon dioxide analyser (Hartmann and Braun URAS 4) sampled continuously from the airway; during the surgical procedure end-tidal $P\text{CO}_2$ was maintained at about 5% by adding carbon dioxide to the inspired gas mixture. The oesophageal temperature was measured with a digital thermistor thermometer and maintained within the range 36–37 °C by under-table heating. The electrocardiogram was recorded from standard limb leads. A 20-cm Teflon catheter was inserted through the left carotid artery and advanced until its tip lay in the ascending aorta. Arterial pressure was measured with a Statham P23 De pressure transducer. Through a left lateral thoracotomy an electromagnetic flow transducer was inserted around the root of the aorta after dissection of the pad of fat. The flow transducer was coupled to a sine wave electromagnetic flowmeter (SEM 230 series, SE Laboratories) to obtain aortic blood flow. Stroke volume was obtained by electronic integration of the flow signal during systole.

For studies of blood-gases in the pulmonary artery, a Portex umbilical cannula was inserted into the pulmonary artery through the infundibulum of the right ventricle and secured in position by a purse-string suture. The blood-gas catheter (EXBC Silastic catheter, Searle, Scientific Research Instruments Corp., Baltimore, U.S.A.), attached to the mass spectrometer (Centronic Medical Gas Analyser MGA 200, T. C. Centronic Ltd, Croydon, U.K.), was also inserted into the pulmonary artery through the infundibulum of the right ventricle and secured in position by a purse-string suture. By palpation of the vessel it was possible to check that the catheter and the umbilical cannula lay side by side in the main pulmonary artery. Six dogs were prepared in this manner.

For studies of blood-gases in the aorta, the blood-gas catheter was inserted into the abdominal aorta via the femoral artery. Four dogs were prepared in this manner.

After the surgical preparation, 1 h was allowed to elapse to obtain a steady state of the circulation and of pulmonary gas exchanges.

The haemodynamic variables (e.c.g., aortic pressure, aortic blood flow, stroke volume) were recorded on an eight-channel ink-jet recorder (Elema-Schonander Mingograph 81). The mass spectrometer signals for oxygen and carbon dioxide were recorded on a Devices hot-stylus recorder.

Blood-gas analysis

Throughout the duration of the experiment, blood samples were drawn anaerobically from the pulmonary artery or the aorta and analysed immediately for $P\text{O}_2$, $P\text{CO}_2$ and pH. $P\text{O}_2$ was measured at 37 °C using Clark-type electrodes calibrated with pure nitrogen, 10% oxygen, room air or 50% oxygen in nitrogen according to the expected values, so that the calibration was for a range close to that of the blood sample. A similar principle was applied to the calibration of the $P\text{CO}_2$ electrode (Severinghaus-type $P\text{CO}_2$ electrode). Three gas mixtures delivered by Wosthoff pumps (Wosthoff OHG, Bochum, Germany) and containing 2%, 5% or 10% carbon dioxide were used. The amplifiers for the electrodes have been described by Hahn (1969, 1971). Temperature connections were applied according to Kelman and Nunn (1966) and a blood-gas difference of 1.04 was applied to $P\text{O}_2$ readings.

Experimental programme

For studies of blood-gases in pulmonary arterial blood, the first stage was to obtain the greatest possible tensions for oxygen and carbon dioxide by using $F\text{I}_{\text{O}_2}$ 0.9 and $F\text{I}_{\text{CO}_2}$ 0.1. The gain of the mass spectrometer was adjusted to full-scale deflection on the hot-stylus recorder. The second stage was to obtain low oxygen and carbon dioxide tensions by reducing $F\text{I}_{\text{O}_2}$ to 0.1 and $F\text{I}_{\text{CO}_2}$ to zero. The gain of the mass spectrometer was usually not altered unless the span of the oxygen and carbon dioxide deflections was inadequate for accurate readings. If an adjustment was necessary, the sequence was repeated. After these initial stages, $F\text{I}_{\text{O}_2}$ and $F\text{I}_{\text{CO}_2}$ were independently and randomly altered and serial readings were taken for periods of up to 5 h. After each change of the inspired gas mixture, sufficient time was allowed for the mass spectrometer signals to stabilize at their new level. Blood samples were then withdrawn and analysed while the mass spectrometer deflections were noted. In three dogs, a second series of readings was obtained after the halothane concentration had been increased from 0.8% to 1.5% in order to study the effect of a reduction of cardiac output on the mass spectrometer signals. For studies in aortic blood, the only difference was that the greatest oxygen and carbon dioxide tensions were obtained at $F\text{I}_{\text{O}_2}$ 0.3 and $F\text{I}_{\text{CO}_2}$ 0.1, otherwise the plan was identical to that described for pulmonary arterial blood.

The mass numbers used for oxygen and carbon dioxide were 32 and 44 respectively. For measurement of gas tensions in the blood phase, the automatic sensitivity control component of the MGA 200 (ASC mode) was not used since the total of the partial pressures could not be known, particularly in the mixed venous blood.

Calibration of the mass spectrometer signals

In order to calculate Po_2 and Pco_2 values from the mass spectrometer recordings, a three-point calibration line was constructed for each experiment. The three points used were the first high, low and mid-range values for respectively Po_2 and Pco_2. From the calibration line, Po_2 and Pco_2 values were obtained for all the subsequent mass spectrometer deflections. It must be noted that during these experiments, each lasting for 4–5 h, there was no attempt to recalibrate the mass spectrometer signals.

RESULTS

Linearity of mass spectrometer responses

During each of the six experiments carried out in the pulmonary artery (mixed venous blood) a linear relationship was observed between mass spectrometer deflections for oxygen and carbon dioxide and measured Po_2 and Pco_2 obtained by conventional blood-gas analysis. Since the span was arbitrary, the slopes differed from experiment to experiment, but the standard error of the slope was always less than 5% of the slope for $P\bar{v}_{O_2}$ and less than 6% for $P\bar{v}_{CO_2}$. The correlation coefficients ranged from 0.975 to 0.995 for $P\bar{v}_{O_2}$ and between 0.985 and 0.995 for $P\bar{v}_{CO_2}$. Examples of the linearity of the response are given in figures 1 and 2.

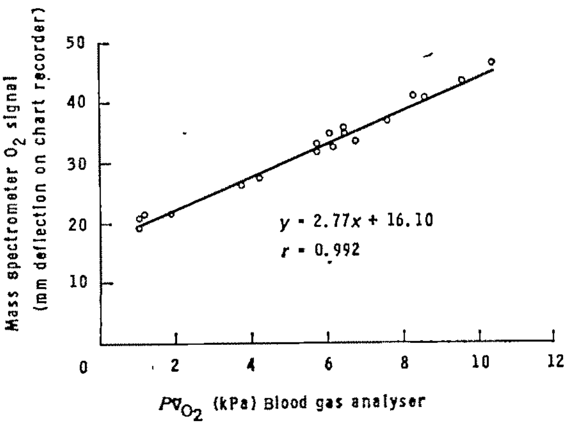

FIG. 1. Relationship between mass spectrometer signals for oxygen and mixed venous oxygen tensions (conventional blood-gas analysis), obtained in one dog. The equation for linear regression and the correlation coefficient are given.

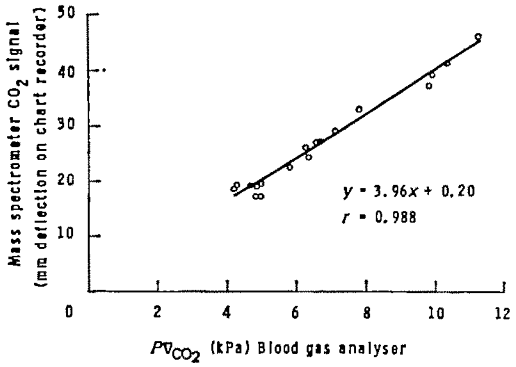

FIG. 2. Relationship between mass spectrometer signals for carbon dioxide and mixed venous carbon dioxide tensions (conventional blood-gas analysis) obtained in one dog. Linear regression and correlation coefficient as in figure 1.

Blood-gas tensions measured by the mass spectrometer

The correlation between blood-gas tensions derived from the mass spectrometer signals and measured blood-gas tensions by conventional analysis are represented in figures 3 and 4 for studies in the pulmonary artery (93 determinations in six dogs) and in figures 5 and 6 for studies in the aorta (29

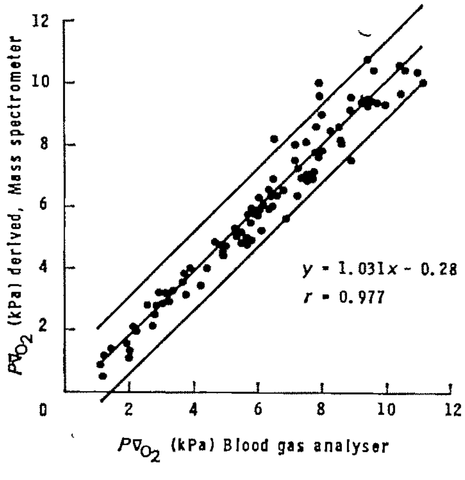

FIG. 3. Relationship between mixed venous oxygen tension derived from the mass spectrometer signals and those obtained by conventional blood-gas analysis. The 93 pairs of values obtained in six dogs are represented, and the straight line regression, the 95% confidence limits, the equation for linear regression and the correlation coefficient are given.

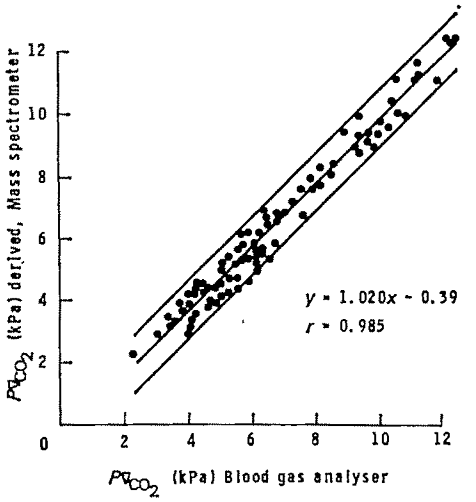

FIG. 4. Relationship between mixed venous carbon dioxide tensions derived from the mass spectrometer signals and those obtained by conventional blood-gas analysis. The 93 pairs of values obtained in six dogs are represented as in figure 5.

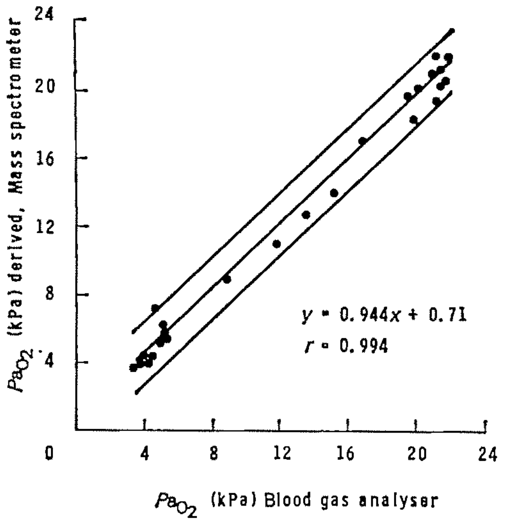

FIG. 5. Relationship between arterial oxygen tensions derived from the mass spectrometer signals and those obtained by conventional blood-gas analysis. The 29 pairs of values obtained in four dogs are represented as in figure 5.

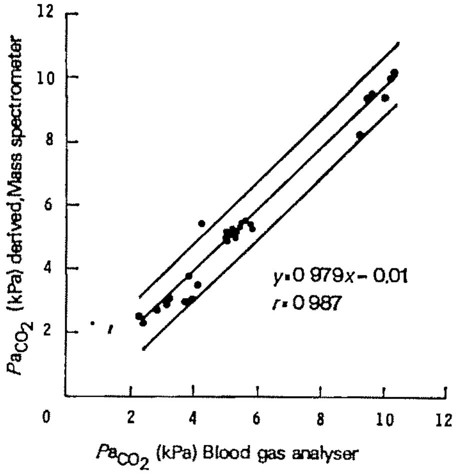

FIG. 6. Relationship between arterial carbon dioxide tensions derived from the mass spectrometer signals and those obtained by conventional blood-gas analysis. The 29 pairs of values obtained in four dogs are represented as in figure 5.

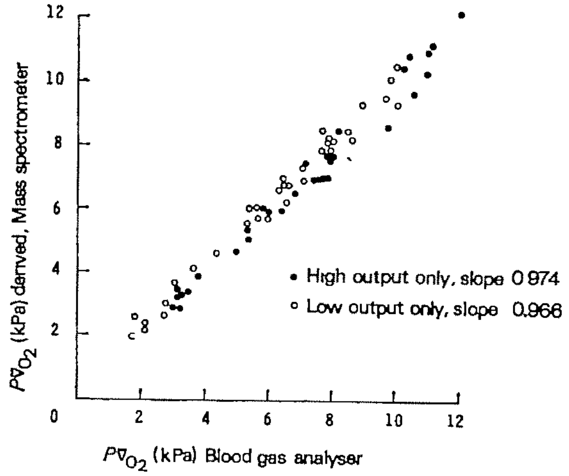

FIG. 7. Relationship between mixed venous oxygen tensions derived from the mass spectrometer signals and those obtained by conventional blood-gas analysis. Two sets of values are represented corresponding to high cardiac output (●) or low cardiac output (○). The slope of the straight line regression is indicated.

determinations in four dogs). For $P\bar{v}_{O_2}$, the slope of the regression line was 1.031 (SEM of slope 0.024); for $P\bar{v}_{CO_2}$, the slope of the regression line was 1.020 (SEM of slope 0.019), the correlation coefficients being 0.977 ($P\bar{v}_{O_2}$) and 0.985 ($P\bar{v}_{CO_2}$). For Pa_{O_2}, the slope of the regression line was 0.944 (SEM of slope 0.020); for Pa_{CO_2}, the slope of the regression line was 0.979 (SEM of slope 0.031). The correlation coefficients were 0.994 (Pa_{O_2}) and 0.987 (Pa_{CO_2}).

Effect of alterations of cardiac output on mass spectrometer readings

During three experiments, cardiac output was deliberately reduced by increasing the inspired halo-

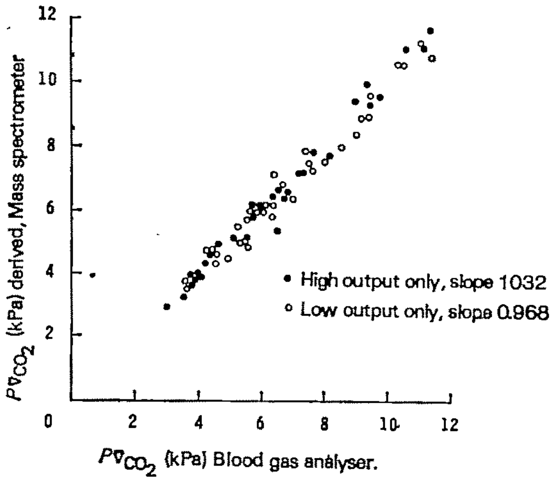

FIG. 8. Relationship between mixed venous carbon dioxide tensions derived from the mass spectrometer signals and those obtained by conventional blood-gas analysis. Two sets of values are represented corresponding to high cardiac output (●) or low cardiac output (○). The slope of the straight line regression is indicated.

thane concentration from 0.8% to 1.5%. This caused a mean reduction of cardiac output by 33%. The observed blood-gas values are represented in figures 7 and 8. For both $P\bar{v}_{O_2}$ and $P\bar{v}_{CO_2}$ the observations made at low cardiac output are interspersed with those made at high cardiac output. However, when individual slopes are considered they tend to be slightly flatter with the lower cardiac output (−0.8% for $P\bar{v}_{O_2}$, −6% for $P\bar{v}_{CO_2}$).

DISCUSSION

A number of authors have reported a linear response of the mass spectrometer when applied to measurements of gas tensions in the blood phase *in vivo*. However, the number of published paired observations (mass spectrometer *v.* conventional blood-gas analysis) is relatively small. Wald and colleagues (1970) have reported nine pairs of values for $P\text{O}_2$ in man; Seylaz and others (1974) have observed a linear correlation between mass spectrometer output and conventional blood-gas analysis in 20 rabbits. It may be that five pairs of determinations were obtained in each animal, but this is not certain. Similarly, Brantigan, Dunn and Albo (1976) refer to a study of seven dogs. In their paper there is one graph showing six pairs of values for $P\text{O}_2$ and $P\text{CO}_2$. Some dogs may have been used only to test the formation of thrombi on the catheter. Pinard, Seylaz and Mamo (1978) are more specific in their evaluation and have performed a total of 19 determinations for $P\text{O}_2$ and 24 determinations for $P\text{CO}_2$ in 12 rabbits. For $P\text{O}_2$, their correlation coefficient is 0.99 in arterial blood and 0.96 in mixed venous blood and for $P\text{CO}_2$ it is 0.89 in arterial blood and 0.91 in mixed venous blood. The latter values are somewhat smaller than our own observations. Finally, Lundgaard, Groenlund and Einer-Jensen (1978) have described 39 determinations of $P\text{O}_2$ only, obtained in three dogs. They observed a linear correlation with a mean deviation between mass spectrometer and conventional blood-gas analysis of −0.2% (SD ± 0.8%).

The results reported here demonstrate that, for oxygen and carbon dioxide, the mass spectrometer may be used in the blood phase for continuous evaluation of blood-gas tensions because of the linearity of its response. Deliberately in this study, enough time was allowed to elapse between readings so that the catheter–mass spectrometer system had time to respond fully to the change of blood-gas tension. The experimental model does not easily allow the study of the response time of the system. From recordings of abrupt changes of oxygen or carbon dioxide concentrations, the response time appears to be of the order of 45–60 s. An *in vitro* calibration loop is presently being developed in order to assess the response time, the flow dependence of the system, and the accuracy of four "subtraction units" designed in order to measure oxygen, nitrous oxide, nitrogen and carbon dioxide simultaneously. This development could open the way to dynamic physiological studies of gas transport during anaesthesia.

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MESURE EN CONTINU *IN VIVO* DES GAZ DU SANG PAR LA SPEKTROMETRIE DE MASSE

RESUME

On a procédé à l'analyse en continu de la tension de l'oxygène et du gaz carbonique dans la phase du sang, pendant des périodes allant de 4 à 5 h, à partir de l'artère pulmonaire (93 déterminations sur six chiens anesthésiés) et de l'aorte (29 déterminations sur quatre chiens anesthésiés). On a utilisé pour cela des cathéters en acier inoxydable recouverts de silastic, attachés à un spectromètre de masse dont les signaux ont été apparentés linéairement aux tensions sang-gaz mesurées par la méthode d'analyse habituelle. Les signaux du spectromètre de masse ont été étalonnés *in vivo* en exposant les animaux à des tensions hautes et basses d'oxygène et de gaz carbonique. Avec un étalonnage *in vivo* de ce genre, les pentes des régressions de la ligne droite pour le spectromètre de masse $P\mathrm{O}_2$ ou $P\mathrm{CO}_2$ par rapport à $P\mathrm{O}_2$ ou $P\mathrm{CO}_2$ par la méthode d'analyse habituelle ont été comprises entre 0,944 et 1,031, alors que l'erreur type des pentes s'est située entre 0,019 et 0,031. Des réductions délibérées du débit cardiaque n'ont eu que peu d'effet sur les lectures du spectromètre de masse.

KONTINUIERLICHE BLUTGASMESSUNG *IN VIVO* DURCH MASSENSPEKTROMETRIE

ZUSAMMENFASSUNG

Durchgeführt wurden kontinuierliche Analysen der Blutgasspannung von Sauerstoff und Kohlendioxyd über Perioden von 4–5 Stunden in der Lungenarterie (93 Bestimmungen in sechs narkotisierten Hunden) und in der Aorta (29 Bestimmungen in vier narkotisierten Hunden). Kunststoffumhüllte Katheter aus rostfreiem Stahl wurden verwendet, die an ein Massenspektrometer angeschlossen waren, dessen Signale dann linear zu den durch konventionelle Analyse gemessenen Blutspannungen in Beziehung gebracht wurden. Diese Signale wurden *in vivo* geeicht, indem die Hunde hohen und niedrigen Sauerstoff- und Kohlendioxydspannungen ausgesetzt wurden. Bei einesolchen *in vivo*-Eichung wurden die Gefälle der geradlinigen Regressionen für Massenspektrometer $P\mathrm{O}_2$ oder $P\mathrm{CO}_2$ bei $P\mathrm{O}_2$ oder $P\mathrm{CO}_2$ durch konventionelle Analyse zwischen 0,944 und 1,031 festgelegt, während die Standardfehlerquelle der Gefälle zwischen 0,019 und 0,031 lag. Bewusste Reduktionen des Herzminutenvolumens hatten kaum Auswirkungen auf die Ablesungen am Massenspektrometer.

MEDICIONES CONTINUAS DE GASES EN LA SANGRE *IN VIVO* POR ESPECTOMETRIA DE MASA

SUMARIO

Se llevó a cabo el análisis continuo sobre periodos de 4–5 h de la tensión de oxígeno y dióxido de carbono en la fase sanguínea en la arteria pulmonar (93 determinaciones en seis perros anestesiados) y en la aorta (29 determinaciones en cuatro perros anestesiados). Se usaron sondas de acero inoxidable revestidas de silástico atadas a un espectómetro de masa. Las señales del espectómetro de masa eran relacionadas linealmente con las tensiones gas-sangre medidas por medio del análisis convencional. Las señales del espectómetro de masa fueron calibradas *in vivo* al exponer los animales a tensiones de alto y bajo oxígeno y de dióxido de carbono. Con tales calibraciones *in vivo*, los gradientes de las regresiones de línea recta para un $P\text{O}_2$ ó $P\text{CO}_2$ del espectómetro de masa frente al $P\text{O}_2$ ó $P\text{CO}_2$ del análisis convencional, variaban entre 0,944 y 1,031 mientras que el error normal de los gradientes oscilaba entre 0,019 y 0,031. Las reducciones deliberadas del volumen-minuto tuvieron muy poco efecto en las lecturas del espectómetro de masa.

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COMPARATIVE HAEMODYNAMIC EFFECTS OF TUBOCURARINE AND METOCURINE IN THE DOG

R. P. ANTONIO, D. M. PHILBIN AND J. J. SAVARESE

SUMMARY

On account of its histamine releasing and ganglion blocking properties tubocurarine is known to have significant haemodynamic effects. Methylation of the compound produces metocurine and should decrease both histamine release and ganglionic blockade. The haemodynamic effects of these two compounds were compared in 10 mongrel dogs anaesthetized with chloralose and morphine. Haemodynamic measurements were made 2 min before and 2, 5, 10 and 20 min after administration of the drugs. Each animal received three doses of each drug with a 2-h rest period between doses: tubocurarine 0.35 (muscle twitch ED$_{95}$), 0.7 and 1.4 mg kg^{-1} and metocurine 0.2 (2 × ED$_{95}$), 0.4 and 0.8 mg kg^{-1}. All doses of tubocurarine produced an increase in heart rate (212, 197 and 212% of control respectively). The mean arterial pressure decreased significantly with 0.7 mg kg^{-1} (48% of control; $P < 0.05$). Metocurine produced no significant haemodynamic effects except for the largest dose (8 × ED$_{95}$). The data suggest that the haemodynamic margin of safety with metocurine in the dog is eight times that of tubocurarine.

In recent years, there has been a renewed interest in the use of dimethyltubocurarine (metocurine) in clinical practice (Savarese, Ali and Antonio, 1977). Structure–activity relationships would predict that the bisquaternary metocurine should produce less histamine release, less profound ganglion blockade and thus lesser haemodynamic side-effects than its monoquaternary analogue tubocurarine. Previous studies have demonstrated that metocurine inhibits neither vagal nor sympathetic activity in cats or monkeys (Hughes and Chapple, 1976a, b) and produces less histamine release (McCullough et al., 1972; Savarese, 1979).

We have compared the haemodynamic effects of metocurine and tubocurarine in dogs.

METHODS

Ten mongrel dogs weighing 17–25 kg were anaesthetized with alpha chloralose 100 mg kg^{-1} and morphine 1 mg kg^{-1} i.v. Arterial pressure was measured in the abdominal aorta via a catheter introduced through the left femoral artery. Central venous, pulmonary artery and pulmonary capillary wedge pressures were recorded via catheters introduced to the right external jugular vein. Heart rate was measured with a tachograph triggered by the arterial pulse wave. Cardiac output was measured by a dye dilution technique using indocyanine green dye and a Beckman recording densitometer. Neuromuscular blockade was measured by the twitch response of the right tibialis anterior muscle stimulated through the peroneal nerve with supramaximal square wave stimuli 0.2 ms in duration at 0.15 Hz. Lung ventilation was controlled to maintain the end-tidal carbon dioxide at 3.5–4.5% recorded by a Beckman LB-1 medical gas analyser.

Following the insertion of the catheters and establishment of a steady state, control measurements were obtained. The animals were then divided arbitrarily into two groups. In group I tubocurarine was given i.v. at three doses—0.35, 0.7 and 1.4 mg kg^{-1} with a 2-h rest period between each dose. Group II received metocurine at doses of 0.2, 0.4 and 0.8 mg kg^{-1} with the same rest period. Following the administration of the drug, haemodynamic measurements were made at 2, 5, 10 and 20 min for each dose in each group.

RESULTS

Haemodynamic data are in tables I and II for group I (tubocurarine) and group II (metocurine) at 2 min. Following the administration of tubocurarine 0.35 mg kg^{-1} there was an increase of 212% from control in heart rate ($P < 0.05$). Central venous pressure decreased to 28% of control ($P < 0.05$) and mean arterial pressure to 70% of control (n.s.). Similar changes

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TABLE I. *Haemodynamic effects of tubocurarine.* $*P<0.05$; $**P<0.01$. HR = heart rate; $\overline{\text{BP}}$ = mean arterial pressure; CO = cardiac output; CVP = central venous pressure; $\overline{\text{PA}}$ = mean pulmonary artery pressure; $\overline{\text{PCW}}$ = mean pulmonary capillary wedge pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance

	0.35 mg kg^{-1}		0.7 mg kg^{-1}		1.4 mg kg^{-1}	
	Control	2 min	Control	2 min	Control	2 min
HR	57	138**	72	135*	70	142**
(beat min^{-1})	±6	±13	±9	±9	±6	±14
$\overline{\text{BP}}$	118	76*	117	54**	114	55*
(mm Hg)	±7	±12	±8	±13	±9	±17
CO	2.48	2.6	2.2	1.3	2.4	1.8
(litre min^{-1})	±0.5	±0.9	±0.4	±0.9	±0.4	±0.8
CVP	4.7	1.3**	5	1.8*	4.6	2**
(mm Hg)	±0.3	±0.2	±0.7	±0.6	±0.7	±0.5
$\overline{\text{PA}}$	12	11	13	11*	18	13
(mm Hg)	±0.3	±0.7	±1.6	±1.6	±1	±2.7
$\overline{\text{PCW}}$	5.5	2	6.0	2.5**	5.6	2.6*
(mm Hg)	±0.4	±0.4	±0.9	±0.6	±0.7	±0.7
SVR	55	40*	63	35**	52	34
(units)	±8	±8	±10	±5	±10	±4
PVR	3.1	5.4*	3.9	8.5*	6.1	8.4
(units)	±0.6	±1.5	±1.0	±2.3	±1.2	±2.6

TABLE II. *Haemodynamic effects of metocurine.* $*P<0.05$; $**P<0.01$. *Abbreviations as for table I*

	0.2 mg kg^{-1}		0.4 mg kg^{-1}		0.8 mg kg^{-1}	
	Control	2 min	Control	2 min	Control	2 min
HR	64	74	68	83*	63	120**
(beat min^{-1})	±7	±8	±9	±6	±8	±13
$\overline{\text{BP}}$	108	107	98	91	108	83*
(mm Hg)	±4	±5	±6	±10	±25	±9
CO	2.4	2.8	2.9	3.2	2.3	2.9
(litre min^{-1})	±0.3	±0.8	±0.6	±0.5	±0.2	±0.5
CVP	3.8	3.5	3.5	2.7*	4.5	2.5*
(mm Hg)	±0.7	±0.7	±0.4	±0.4	±0.8	±0.4
$\overline{\text{PA}}$	14	14	15	15	15.5	14
(mm Hg)	±1	±1	±1.7	±1.7	±1	±1.8
$\overline{\text{PCW}}$	6.7	6.2	6.3	5.8	6.8	4*
(mm Hg)	±1	±1	±0.5	±0.7	±0.7	±1.1
SVR	48	42	39	33*	47	33**
(units)	±6	±6	±8	±6	±5	±6
PVR	3.4	3.2	3.7	3.5	4.1	4.1
(units)	±0.7	±0.7	±1.3	±1.2	±0.5	±0.6

occurred with 0.7 and 1.4 mg kg^{-1}. There were no significant changes in cardiac output.

In group II, there were no significant changes throughout the study period at doses of 0.2 mg kg^{-1}. With 0.4 mg kg^{-1} there was a significant increase in heart rate and decrease in systemic vascular resistance. Only at 0.8 mg kg^{-1} were changes, comparable with those obtained with low-dose tubocurarine, noted.

DISCUSSION

The chloralose-morphine anaesthetic technique was chosen to produce a preparation with high autonomic tone and slow baseline heart rate, a vagotonic preparation analogous to the clinical findings in adult man.

The initial dose of tubocurarine (0.35 mg kg^{-1}) was chosen to represent approximately ED_{95} for neuromuscular blockade in the dog. Subsequent doses were then two and four times ED_{95} respectively.

The initial dose of metocurine (0.2 mg kg^{-1}) represents twice ED_{95} for this drug in the dog (Mogey and Trevan, 1950; Donlon, Ali and Savarese, 1974) with subsequent doses thus representing four and eight times ED_{95}.

It was apparent that the initial dose of tubocurarine (ED_{95}) and all subsequent doses produced profound haemodynamic changes within 2 min of administration. Such responses are well documented clinically. It was apparent also that no significant haemodynamic change occurred with metocurine at two or four times ED_{95}. Only at eight times the neuromuscular ED_{95} did metocurine produce changes similar to those noted for tubocurarine at ED_{95}. These data demonstrate that the safety margin for haemodynamic change after metocurine in the dog is therefore eight times greater than that of tubocurarine.

Although metocurine has been available since its synthesis by King in 1935, it has not been popular in clinical use despite early studies suggesting less histamine release (Wilson, Gordon and Raffan, 1950) and little effect on arterial pressure (Stoelting, Graf and Vieira, 1948). More recent studies have confirmed the absence of significant autonomic effects both in animals (Hughes and Chapple, 1976a; Savarese, 1979) and man (Savarese, Ali and Antonio, 1977; Zaiden et al., 1977). The unpopularity may be in some part the result of difficulty in synthesizing the drug and maintaining batch-to-batch potency (Mogey and Trevan, 1950). This is no longer the case (Savarese, Ali and Antonio, 1977).

While the neuromuscular blocking action of metocurine does not differ substantially from those of other non-depolarizing agents, its cardiovascular effects are different and this may offer a distinct advantage. Metocurine does not block the cardiac muscarinic receptors (Hughes and Chapple, 1976b; Savarese, 1979) and thus does not produce a tachycardia (Stoelting, 1974) unless histamine release occurs. This appears to require significantly greater doses than with tubocurarine. This, and its weaker ganglionic-blocking action, reduces the risk of hypotension.

The wide margin of safety for haemodynamic effects between metocurine and tubocurarine shown in this study suggests that the former may be the relaxant of choice for patients with cardiac disease. Its weak ganglion-blocking and histamine releasing properties and its lack of vagolytic (cardiac muscarinic) blocking action may render it appropriate for patients with coronary artery disease where tachycardia and hypotension may result in myocardial ischaemia.

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COMPARAISON DES EFFETS HEMODYNAMIQUES DE LA TUBOCURARINE ET DE LA METOCURINE CHEZ LE CHIEN

RESUME

On sait que la tubocurarine produit des effets hémodynamiques significatifs en raison des propriétés qu'elle possède et qui sont à l'origine du dégagement d'histamine et du blocage des ganglions. Le traitement au méthyle de ce composé produit de la métocurine et celle-ci devrait permettre de diminuer aussi bien le dégagement d'histamine que le blocage des ganglions. On a procédé à une comparaison des effets hémodynamiques de ces deux composés sur 10 chiens bâtards anesthésiés à l'aide de chloralose et de morphine. Les mesures hémodynamiques ont été prises 2 min avant et 2, 5, 10 et 20 min après l'administration des médicaments. Chaque animal a reçu trois doses de chacun des médicaments, avec une période de repos de 2 h entre les doses: tubocurarine 0,35 (crispation du muscle ED_{95}), 0,7 et 1,4 mg kg^{-1} et métocurine 0,2 (2 × ED_{95}), 0,4 et 0,8 mg kg^{-1}. Toutes les doses de tubocurarine ont produit une augmentation de la fréquence cardiaque (respectivement 212, 197,

212% des valeurs témoins). La pression artérielle moyenne a diminué d'une manière significative avec 0,7 mg kg^{-1} (48% de la valeur témoin; $P < 0{,}05$). La métocurine n'a produit aucun effet hémodynamique significatif, sauf en ce qui concerne la plus forte dose ($8 \times ED_{95}$). Les données obtenues laissent penser que chez le chien la marge de sécurité hémodynamique de la métocurine est de huit fois celle de la tubocurarine.

VERGLEICHSWEISE HÄMODYNAMISCHE WIRKUNGEN VON TUBOCURARIN UND METOCURIN BEI HUNDEN

ZUSAMMENFASSUNG

Aufgrund seiner Eigenschaften der Freigabe von Histamin und der ganglionischen Blockierung weiss man, dass Tubocurarin wesentliche hämodynamische Wirkungen hat. Methylisierung der Verbindung erzeugt Metocurin, und sollte sowohl die Histamin-Freigabe als auch die ganglionische Blockierung herabsetzen. Die hämodynamischen Wirkungen dieser beiden Verbindungen wurden an zehn Mischrassen-Hunden getestet, die mit Chloralose und Morphium narkotisiert waren. Hämodynamische Messungen wurden 2 min vor und 2, 5, 10 und 20 min nach Verabreichung der Drogen durchgeführt. Jedes Tier erhielt drei Dosen jeder Droge, mit einer zweistündigen Rastperiode zwischen jeder Dosis: 0,35 (Muskelzuckung ED_{95}), 0,7 und 1,4 mg kg^{-1} Tubocurarin, und 0,2 ($2 \times ED_{95}$), 0,4 und 0,8 mg kg^{-1} Metocurin. Alle Dosen von Tubocurarin bewirkten Anstiege des Herzminutenvolumens (212, 197 und 212% des Kontrollwertes), und der mittlere arterielle Druck sank wesentlich mit 0,7 mg kg^{-1} (48% des Kontrollwertes von $P < 0{,}05$). Metocurin bewirkte keine wesentlichen hämodynamischen Effekte, ausser in der grössten Dosis ($8 \times ED_{95}$). Diese Angaben lassen erkennen, dass die hämodynamische Sicherheitsgrenze von Metocurin bei Hunden achtmal höher liegt wie die von Tubocurarin.

EFECTOS HEMODINAMICOS COMPARATIVOS DE LA TUBOCURARINA Y DE LA METOCURINA EN EL PERRO

SUMARIO

Se sabe que, a raíz de sus propiedades de bloqueo gangliónico y de producción de histamina, la tubocurarina tiene efectos hemodinámicos significativos. La metilación del compuesto produce metocurina y debería reducir tanto la producción de histamina como el bloqueo gangliónico. Se compararon los efectos hemodinámicos de estos dos compuestos en 10 perros cruzados anestesiados con cloralosa y morfina. Se realizaron mediciones hemodinámicas 2 min antes y 2, 5, 10 y 20 min después de la administración de las substancias. Cada animal recibió tres dosis de cada substancia con un periodo de descanso de 2 h entre cada dosis: 0,35 mg (contracción muscular ED_{95}), 0,7 mg y 1,4 mg kg^{-1} de tubocurarina y 0,2 mg ($2 \times ED_{95}$), 0.4 mg y 0,8 mg kg^{-1} de metocurina. Todas las dosis de tubocurarina causaron un aumento del ritmo cárdiaco (212, 197, 212% del control, respectivamente). La presión arterial media disminuyó de manera significativa con 0,7 mg kg^{-1} (48% del control $P < 0{,}05$). La metocurina no tuvo ningún efecto hemodinámico significativo, salvo en mayor dosis ($8 \times ED_{95}$). Estos datos sugieren que el margen hemodinámico de seguridad con metocurina en el perro es ocho veces mayor que el de la tubocurarina.

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OXYGEN TRANSPORT DURING DOPAMINE INFUSION IN DOGS

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SUMMARY

Catecholamines increase not only oxygen delivery to tissues but also oxygen consumption ($\dot{V}O_2$). The effect of an infusion of dopamine hydrochloride has been studied at two doses, each in six dogs. Dopamine 10 μg kg⁻¹ min⁻¹ caused an increase in haemoglobin concentration and altered cardiac output, oxygen availability and total body oxygen consumption such that oxygen availability ratio increased and ($Ca_{O_2} - C\bar{v}_{O_2}$) decreased although these changes were not statistically significant. Dopamine 30 μg kg⁻¹ min⁻¹ increased ($P < 0.05$) heart rate, haemoglobin concentration and Ca_{O_2} and significantly reduced stroke volume and V_D/V_T. Although oxygen availability increased, increases in oxygen consumption were greater and this resulted in a statistically insignificant reduction in oxygen availability ratio and an increase in ($Ca_{O_2} - C\bar{v}_{O_2}$). Terminating the dopamine infusion resulted in significant ($P < 0.05$) decreases in cardiac output, $P\bar{v}_{O_2}$, Ca_{O_2}, oxygen availability and oxygen consumption and an increase in ($Ca_{O_2} - C\bar{v}_{O_2}$). It was concluded that maximum oxygen delivery occurs at a lower dose than that required to produce the maximum increase in oxygen consumption.

Dopamine has been shown to be effective in improving cardiac output in a wide variety of shock conditions (Goldberg, McDonald and Zimmerman, 1963; Loeb et al., 1971; Thompson, 1977). In addition to its activity at specific dopamine receptors, dopamine has both alpha- and beta-adrenergic agonist activity (Goldberg, 1972). Catecholamines have profound effects on intermediary metabolism which result in an increased total body oxygen consumption (Himms-Hagen, 1967) and may adversely affect pulmonary gas exchange (Finlay, Wightman and Sykes, 1970). Accordingly we have investigated the overall effects of dopamine on oxygen transport at two different doses. The results of metabolic studies will be reported separately (Hall, Young and Scott, 1979).

METHODS

Twelve cross-bred dogs (weight 11.7–34.2 kg) were studied. They were fed on a standard laboratory diet and allowed water *ad libitum* for at least 3 days before each experiment. The animals were allocated randomly to either a small-dose (dopamine HCl 10 μg kg⁻¹ min⁻¹) or a large-dose (dopamine HCl 30 μg kg⁻¹ min⁻¹) treatment group.

The dogs were anaesthetized with thiopentone 15–20 mg kg⁻¹ and pentobarbitone 5–7 mg kg⁻¹. They were placed in the supine position, a cuffed tube was inserted to the trachea and the lungs were ventilated with ambient air using a Cape Ventilator. The respiratory frequency was maintained at 15 b.p.m. Airway pressure was monitored throughout and whenever there was evidence of respiratory muscle activity (usually negative airway pressure during expiration or sometimes an increase in positive end-inspiratory pressure) incremental doses of thiopentone 5 mg kg⁻¹ were given in order to maintain completely passive ventilation. Such increments of thiopentone were given at least 10 min before cardiorespiratory observations were made. During an experiment lasting 3.5–4 h, the average number of incremental doses administered was 3.9.

Catheters for pressure measurement and blood sampling were placed in the aorta via the left femoral artery and in the main pulmonary artery via the right jugular vein. A Swan–Ganz catheter was passed into a pulmonary artery from the left jugular vein for measurement of pulmonary capillary wedge pressure. Pressures were recorded continuously using strain gauges, the amplified outputs displayed on a six-channel hot-wire chart recorder (Devices M19). The strain gauges were calibrated against a column of saline. Mean pressures were derived electronically.

Cardiac output was determined by indocyanine green dye dilution. Dye was injected into the right atrium and sampled from the aorta. The output from the densitometer (Gilford 103) was recorded and the cardiac output calculated from the co-ordinates of the resulting curve by the method of Simons and White (1976). The mean value of at

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least two satisfactory curves was used. Heart rate was measured by counting the aortic pressure pulses during a 15-s period recorded at a paper speed of 500 mm min^{-1}.

Expired gas was separated from the gas compressed in the ventilator tubing by a collect valve (Sykes, 1969). It was passed through a mixing chamber and the volume measured using a calibrated dry-gas meter. Mixed expired oxygen concentration was determined using a paramagnetic oxygen analyser (Servomex 101A); end-tidal and mixed expired carbon dioxide concentration using an infra-red analyser (Hartmann-Braun URAS 4). During the gas sampling arterial and mixed venous blood samples were drawn into heparinized syringes and analysed immediately. Po_2, Pco_2 and pH were measured in duplicate on separate electrode systems (ABL 1 and PHM-1, Radiometer, Copenhagen). The oxygen content of arterial and mixed venous blood (Ca_{O_2}, $C\bar{v}_{O_2}$) was determined directly. Oxygen was displaced from haemoglobin by carbon monoxide and measured in an electrolytic cell (Lex-O_2-Con, Lexington Instruments Corp.). Haemoglobin concentration was determined using the cyanmethaemoglobin method.

Procedure

Approximately 60 min was required for preparation following induction of anaesthesia. During this period the tidal volume delivered by the ventilator was adjusted so that the end-tidal Fco_2 was in the range 4.5–5.0 vol%. At time zero sodium chloride 0.15 mol $litre^{-1}$ delivered from a calibrated pump (31.4 ml h^{-1}) was infused via a catheter inserted to the inferior vena cava. The animals' lungs were hyperinflated twice (airway pressure > 25 cm H_2O). Between 5 and 10 min any final adjustment of the ventilation was made. After 15 min a venous blood sample for biochemical studies was drawn and the blood replaced with an equal volume of dextran 70. Between 25 and 30 min the cardiovascular and respiratory measurements were performed. At 30 min a second venous blood sample was taken (fig. 1) and the infusion changed immediately to dopamine HCl (Intropin, Arnar Stone) either 10 $\mu g\ kg^{-1}\ min^{-1}$ or 30 $\mu g\ kg^{-1}\ min^{-1}$ in sodium chloride 0.15 mol $litre^{-1}$.

This infusion was continued for 1 h during which the sequence of events described above was repeated twice. Finally, sodium chloride 0.15 mol $litre^{-1}$ was infused at the same rate for a further 1 h and two further sets of measurements were obtained (fig. 1).

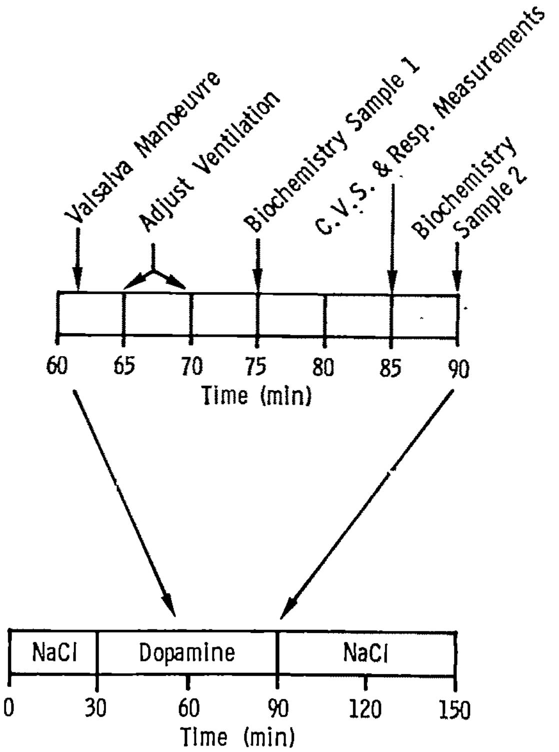

FIG. 1. Schematic representation of the experimental procedure. Top: Events occurring during each 30-min period of the experiment. Bottom: Time sequence of the control (sodium chloride 0.15 mol $litre^{-1}$) and drug infusions. C.V.S. = cardiovascular system.

Calculations

Correction factors were applied for temperature changes and blood-gas factors of the oxygen electrodes. The derived variables were computed using standard respiratory formulae. Venous admixture was calculated using the measured arteriovenous oxygen content difference ($Ca_{O_2} - C\bar{v}_{O_2}$) as described previously (Scott et al., 1978). Oxygen availability was calculated as the product of arterial oxygen content (Ca_{O_2}) and cardiac output, oxygen availability ratio as the ratio of oxygen availability to oxygen consumption.

Statistical comparisons were made as follows: (a) in each dose group the mean value of a variable at any time was compared with the mean value at each other time using two-way analysis of variance and Student's *t* test for paired data values; (b) between dose groups the mean value of a variable at any time was compared with the mean value of that variable at the same time but a different dose using Student's two-sample t test. $P < 0.05$ was considered statistically significant.

RESULTS

The mean weight ± SD of dogs in the small-dose group was 24.2 ± 7.5 kg, while in the large-dose group it was 19.3 ± 6.8 kg. Other differences occurred between the initial control values of the two groups but none was statistically significant. Thus cardiac output was smaller whilst oxygen consumption and $(Ca_{O_2}-C\bar{v}_{O_2})$ were greater in the small-dose treatment group (tables I, III). Initial control values of venous admixture $(\dot{Q}s/\dot{Q}t)$ and deadspace/tidal volume ratio (V_D/V_T) were smaller in the small-dose animals than those in the large-dose ones (table II).

Cardiac output (table I).

After 30 min infusion of dopamine the cardiac output had increased in five of six dogs in the small-dose group, whereas in the large-dose group an increase occurred in only two of six. At the same time $P\bar{v}_{O_2}$ (table I) increased in both groups. During the second 30 min of dopamine infusion, the mean value of cardiac output and $P\bar{v}_{O_2}$ decreased so that at the end of the dopamine infusion these variables were equal to or less than initial control values.

In the small-dose group both the decrease in cardiac output $(P = 0.002)$ and $P\bar{v}_{O_2}$ $(P = 0.014)$ were statistically significant, as was the decrease in $P\bar{v}_{O_2}$ in the large-dose group $(P = 0.017)$. Stopping the dopamine infusion resulted in further significant $(P < 0.05)$ decreases in cardiac output. At this time mean systemic and pulmonary artery pressures were also reduced.

Heart rate

Thirty minutes after commencing the infusion of dopamine, heart rate increased in both groups. With the large dose the magnitude of the increase was approximately three times that with the small dose. Although stroke volume increased slightly in response to dopamine 10 μg kg^{-1} min^{-1} it decreased $(P < 0.05)$ during 30 μg kg^{-1} min^{-1}. In the second group the increase in heart rate was maintained throughout the infusion of dopamine and decreased to initial control values when the dopamine infusion was discontinued.

Ventilation and gas exchange (table II)

During the infusion of dopamine oxygen consumption and carbon dioxide output increased compared with initial control values, reaching peak values after 60 min. The average increase in oxygen consumption (table III) during dopamine 10 μg kg^{-1} min^{-1} was 24% of initial control value and that during dopamine 30 μg kg^{-1} min^{-1} was 60%. The concomitant changes in carbon dioxide output were 26% and 49% respectively. Oxygen consumption and carbon dioxide output decreased when dopamine was discontinued, but still had not reached initial control values 60 min later.

During the infusion of the small dose, $\dot{V}_E$ was increased by an increase in V_T and Pa_{CO_2} did not alter significantly. With the large-dose, however, the initial mean value of Pa_{CO_2} was greater than desired. After 30 min with the large dose, $\dot{V}_E$ had been increased and Pa_{CO_2} had decreased. On cessation of dopamine infusion $\dot{V}_T$ was reduced and there were no major changes in Pa_{CO_2}.

Arterial hydrogen ion concentration $[H^+]a$ increased throughout the infusion of both doses of dopamine in comparison with control values. As this was accompanied by either no change or a decrease in Pa_{CO_2}, it indicates an increase in the non-respiratory component of $[H^+]a$. This tendency was reversed when dopamine was stopped although cardiac output was decreasing and $(Ca_{O_2}-C\bar{v}_{O_2})$ was increasing.

The infusion of the small dose of dopamine did not alter V_D/V_T, $(PA_{O_2}-Pa_{O_2})$ or $\dot{Q}s/\dot{Q}t$ in comparison with control values (table II). With the large dose V_D/V_T decreased significantly $(P = 0.02)$ after 30 min, but increased significantly $(P = 0.01)$ during the second 30 min of infusion. With both doses $\dot{Q}s/\dot{Q}t$ did not change significantly. Cessation of the infusion resulted in a significant $(P < 0.05)$ decrease in $\dot{Q}s/\dot{Q}t$ in both groups.

Oxygen transport (table III)

Arterial oxygen tension did not change significantly during or after the infusion of either dose. Infusion of the small dose was associated with an increase (not statistically significant) in haemoglobin concentration (Hb) which remained throughout the 60 min and decreased again when dopamine was stopped. Infusion of the large dose resulted in a significant $(P = 0.005)$ increase in Hb after 30 min, but after 60 min haemoglobin concentration had decreased significantly $(P = 0.046)$ compared with the peak value. There was a further decrease in haemoglobin to control values when dopamine was withdrawn. The increase in oxygen carrying capacity, which resulted from these changes in haemoglobin, produced parallel changes in Ca_{O_2}.

TABLE I. *Mean ± SEM of some pulmonary gas exchange variables before, during and after an infusion of dopamine* 10 *or* 30 μ*g kg*$^{-1}$ *min*$^{-1}$ *each in six dogs. Mean values which differ significantly* ($P < 0.05$) *from those at other times are indicated by the postscripts*: a = *different from initial control*; b = *different from* 30 *min dopamine*; c = *different from* 60 *min dopamine*; d = *different from* 30 *min after stopping dopamine*; e = *different from* 60 *min after dopamine*

	Dopamine 10 μg kg^{-1} min^{-1} (six dogs)					Dopamine 30 μg kg^{-1} min^{-1} (six dogs)				
	Initial control	During dopamine		After dopamine		Initial control	During dopamine		After dopamine	
		30 min	60 min	30 min	60 min		30 min	60 min	30 min	60 min
Cardiac output (litre min^{-1})	2.89^{d}	3.91^{cde}	2.83^{bde}	1.57^{abc}	1.66^{bc}	3.74^{de}	3.92	3.39^{de}	2.35^{ac}	2.35^{ac}
	±0.44	±0.58	±0.50	±0.28	±0.28	±0.34	±0.80	±0.56	±0.48	±0.42
Mixed venous oxygen tension (kPa)	6.2^{de}	6.4^{cde}	6.2^{bde}	5.2^{abc}	5.0^{abc}	6.2^{de}	6.5^{cde}	6.0^{bde}	5.0^{abc}	4.8^{abc}
	±0.15	±0.26	±0.28	±0.19	±0.09	±0.19	±0.17	±0.13	±0.09	±0.29
Mean systemic arterial pressure (kPa)	21.2	22.6	21.1	17.5	18.8	19.4^{de}	20.5	20.0	16.0^{a}	16.7^{a}
	±1.5	±2.1	±1.5	±2.8	±2.4	±0.9	±1.4	±1.3	±1.6	±1.7
Mean pulmonary arterial pressure (kPa)	1.75	1.85	1.85	1.55	1.75	1.75	2.20	2.15	2.00	1.70
	±0.29	±0.35	±0.36	±0.24	±0.24	±0.11	±0.20	±0.16	±0.20	±0.10
Mean pulmonary capillary wedge pressure (kPa)	0.40	0.40	0.35	0.30	0.50	0.40	0.55	0.40	0.60	0.45
	±0.12	±0.10	±0.09	±0.12	±0.17	±0.09	±0.09	±0.07	±0.08	±0.10
Heart rate (beat min^{-1})	175	230	168	172	138	176^{bc}	263^{ade}	240^{ade}	173^{bc}	168^{bc}
	±23	±31	±24	±20	±14	±5	±18	±17	±10	±9
	($n = 4$)	($n = 5$)	($n = 5$)	($n = 5$)	($n = 5$)					
Stroke volume (ml)	19	22	17	10	12	22^{bcde}	15^{a}	15^{a}	15^{a}	15^{a}
	±3.6	±5.8	±3.9	±3.7	±2.8	±2.2	±3.4	±2.8	±3.6	±3.3
	($n = 4$)	($n = 5$)	($n = 5$)	($n = 5$)	($n = 5$)					

The combination of an increased cardiac output and Ca_{O_2} resulted in an increase in oxygen availability after 30 min in both groups. From this peak value oxygen availability decreased significantly ($P = 0.007$) during the second half of the infusion of dopamine in the small dose. After 60 min infusion of dopamine, oxygen availability decreased to initial control values in both groups.

These increases in oxygen availability were achieved only at the cost of dose-related increases in oxygen consumption. This resulted in an increase in oxygen availability ratio during the first 30 min with the small dose, followed by a decrease to control values after 60 min. However, with the large dose oxygen availability ratio decreased markedly after both 30 min and 60 min of infusion. In the latter group these decreases were accompanied by an increase in ($Ca_{O_2} - C\bar{v}_{O_2}$) which was significant ($P = 0.001$) at 60 min. Discontinuing the infusion of dopamine halved oxygen availability ratio with the small dose and increased ($Ca_{O_2} - C\bar{v}_{O_2}$) while with the large dose there was no further significant increase in ($Ca_{O_2} - C\bar{v}_{O_2}$).

DISCUSSION

Initiation of dopamine infusion

Haemodynamic changes. Agreement exists on the haemodynamic response to dopamine under a wide variety of experimental conditions. Thus dose-

TABLE II. *Mean ± SEM of some pulmonary gas exchange variables before, during and after an infusion of dopamine* 10 *or* 30 $\mu g\ kg^{-1}\ min^{-1}$ *each in six dogs. Mean values which differ significantly* ($P < 0.05$) *from those at other times are indicated by the postscripts*: a = *different from initial control*; b = *different from 30 min dopamine*; c = *different from 60 min dopamine*; d = *different from 30 min after stopping dopamine*; e = *different from 60 min after dopamine*

	Dopamine 10 $\mu g\ kg^{-1}\ min^{-1}$ (six dogs)					Dopamine 30 $\mu g\ kg^{-1}\ min^{-1}$ (six dogs)				
	Initial control	During dopamine		After dopamine		Initial control	During dopamine		After dopamine	
		30 min	60 min	30 min	60 min		30 min	60 min	30 min	60 min
Minute volume (litre min^{-1})	6.53 ±0.93	7.33 ±1.17	7.17 ±1.20	6.59 ±0.84	6.04 ±0.86	5.08 ±0.47	6.85 ±1.14	6.84^{d} ±0.86	5.83^{c} ±0.57	5.91 ±0.53
Carbon dioxide production (mmol min^{-1})	6.00 ±0.75 ($n = 5$)	7.45 ±1.54 ($n = 5$)	7.60^{e} ±1.29	6.90 ±1.05 ($n = 5$)	6.45^{c} ±1.02	4.90^{c} ±0.28	7.30^{e} ±1.05	7.30^{ade} ±0.81	5.65^{c} ±0.41	5.25^{bc} ±0.38
Pa_{CO_2} (kPa)	4.95 ±0.15 ($n = 5$)	4.70 ±0.13	4.90 ±0.17	4.80 ±0.14	4.80 ±0.18	5.55 ±0.33	4.75 ±0.25	5.25 ±0.29	5.10 ±0.16	4.90 ±0.08
Arterial [H^+] (nmol $litre^{-1}$)	45.0 ±1.3	46.5 ±1.7	48.5 ±0.8	45.5 ±1.6	45.5 ±1.1	50.0 ±2.5	50.0 ±1.4	54.0 ±2.2	50.5 ±1.3	48.5 ±1.6
V_D/V_T (%)	37 ±3 ($n = 4$)	34 ±3 ($n = 5$)	38 ±4 ($n = 5$)	36 ±3 ($n = 5$)	36 ±3	46^{b} ±4	35^{acde} ±1	41^{b} ±2	43^{b} ±3	46^{b} ±3
Pulmonary venous admixture (%)	14^{de} ±3	14^{de} ±2	13^{de} ±3	7^{abc} ±2	6^{abc} ±1	20^{de} ±3	17^{e} ±2	20^{de} ±3	12^{ac} ±3	9^{abc} ±3
($PA_{O_2} - Pa_{O_2}$) (kPa)	3.5 ±0.3 ($n = 5$)	3.3 ±0.2 ($n = 5$)	3.3 ±0.3	2.7 ±0.4	2.9 ±0.3	3.3 ±0.4	3.4 ±0.5	3.3 ±0.4	3.3 ±0.3	3.0 ±0.3

related increases in left ventricular dP/dt max are found in conscious dogs (Vatner, Millard and Higgins, 1973), in anaesthetized intact dogs (Black and Rollett, 1968; Bruckner et. al, 1977) and following vagotomy in open-chest dogs (McDonald and Goldberg, 1963; Lumley, Broadley and Levy 1977) in doses up to 40 $\mu g\ kg^{-1}\ min^{-1}$. These results have been confirmed recently in our own laboratory in dogs with paced heart rate and controlled afterload. Quantitative differences that occur may result from the very varied conditions employed. While dopamine may be expected to improve the inotropic state of the myocardium, the effect on cardiac output will depend, not only on the control state of inotropy, but also on changes in the ventricular filling pressures and pulmonary and systemic vascular resistances. Our finding, that after 30 min cardiac output was increased more consistently with the small dose, may have resulted from alterations in these factors which were not controlled during our experiments.

TABLE III. *Mean ± SEM of some pulmonary gas exchange variables before, during and after an infusion of either dopamine 10 or 30 μg kg^{-1} min^{-1} each in six dogs. Mean values which differ significantly ($P < 0.05$) from those at other times are indicated by the postscripts*: a = *different from initial control*; b = *different from 30 min dopamine*; c = *different from 60 min dopamine*; d = *different from 30 min after stopping dopamine*; e = *different from 60 min after dopamine*

	Dopamine 10 μg kg^{-1} min^{-1} (six dogs)					Dopamine 30 μg kg^{-1} min^{-1} (six dogs)				
	Initial control	During dopamine		After dopamine		Initial control	During dopamine		After dopamine	
		30 min	60 min	30 min	60 min		30 min	60 min	30 min	60 min
Pa_{O_2} (kPa)	11.1 ±0.4	11.2 ±0.3	11.0 ±0.5	11.8 ±0.7	11.4 ±0.4	10.1 ±0.5	10.9 ±0.3	10.0 ±0.3	10.4 ±0.4	11.0 ±0.5
Haemoglobin concentration (g dl^{-1})	15.4 ±1.5	16.7 ±1.8	16.8 ±1.8	15.9 ±1.7	15.1 ±2.0	15.4^{bc} ±0.9	18.0^{acde} ±0.6	17.1^{abc} ±0.8	14.6^{b} ±1.0	13.5^{bc} <0.8
Ca_{O_2} (mmol litre^{-1})	9.5 ±0.7	10.5^{de} ±1.1	10.2^{de} ±1.0	9.1^{bc} ±0.9	8.4^{bc} ±0.9	8.1^{b} ±0.6	9.8^{de} ±0.5	9.3^{de} ±0.7	7.1^{bc} ±0.6	7.1^{bc} ±0.5
Oxygen availability (mmol min^{-1})	28^{de} ±5	43^{cde} ±11	31^{bd} ±8	15^{abc} ±4	13^{ab} ±2	31^{de} ±4	40^{de} ±10	33^{de} ±8	17^{abc} ±4	17^{abc} ±4
Oxygen consumption (mmol min^{-1})	6.9 ±0.9 ($n = 5$)	8.4^{e} ±1.5 ($n = 5$)	8.6^{e} ±1.3	7.6 ±1.0	7.6^{b} ±1.1	5.8^{c} ±0.4	9.0 ±1.1	9.6^{ade} ±1.2	7.4^{c} ±0.7	6.5^{c} ±0.5
Oxygen availability ratio	3.6 ($n = 5$)	4.0 ($n = 5$)	3.4	1.8	1.8	5.2	4.2	3.3	2.4	2.7
($Ca_{O_2} - C\bar{v}_{O_2}$) (mmol litre^{-1})	2.6 ±0.3	2.5^{de} ±0.2	2.8^{de} ±0.4	3.9^{b} ±0.7	3.6^{b} ±0.8	2.1^{cd} ±0.2	2.7 ±0.2	2.8^{a} ±0.2	3.1^{a} ±0.3	2.8 ±0.3

Previous reports have varied with regard to the changes in heart rate in response to dopamine. Simultaneous measurement of inotropic (Walton–Brodie Strain Gauge) and chronotropic dose-response curves in open-chest dogs has shown that the inotropic response curve lies to the left of the chronotropic (Endoh, 1975; Lumley, Broadley and Levy, 1977). This is consistent with our finding and that of others that these are dose-related increases in heart rate during infusion of dopamine. It is equally consistent with the finding that there is no change in heart rate when only small doses were used (Black and Rollett, 1968; Wintroub et al., 1969).

Ventilation and gas exchange. Despite the intention to control ventilation to minimize changes in Pa_{CO_2}, two dogs receiving the large dose had an unexpectedly increased Pa_{CO_2} at the end of the initial control infusion. There was no satisfactory explanation for this, other than that initial ventilator settings had been made incorrectly, on the basis of end tidal carbon dioxide measurements during the first 10 min. This increase of Pa_{CO_2} is a possible explanation for the higher average control cardiac output in the large dose group. However, application of correction factors for the alteration in pH and Pa_{CO_2} (Carson et al., 1965) did not alter the trend of the data. The readjustment of arterial Pa_{CO_2} may have affected carbon dioxide output during the first 30 min of infusion of dopamine. A new equilibrium would have been reached within 20 min after readjustment, so sampling should have taken place during steady-state conditions. For these reasons it was decided not to exclude data from these animals.

We cannot find other data on oxygen consumption changes in response to dopamine infusion, although myocardial oxygen consumption is known to increase in proportion to left ventricular work (Bruckner et al., 1977). Other synthetic and endogenous catecholamines are known to increase oxygen consumption, although the mechanism by which this occurs is not clear (Himms-Hagen, 1967). Our finding was that both oxygen consumption and carbon dioxide output increased markedly in response to dopamine.

The only major change which occurred in respiratory variables in response to dopamine was a decrease in V_D/V_T during the first 30 min of infusion of the large dose. This probably resulted from haemodynamic alterations as it occurred in five dogs in which a small increase in mean pulmonary artery pressure occurred at this time.

Other studies have shown that dopamine may increase pulmonary venous admixture (Berk et al., 1977; Rapin et al., 1977), and recent work shows that dopamine also depresses pulmonary hypoxic vasoconstrictor responses in the dog (Marin et al., 1979). During this study control values of venous admixture were generally high and this may explain why further increases in venous admixture did not occur.

Oxygen transport. Haemoglobin concentration increased during infusion of dopamine in a dose-related manner. Splenic contraction and autotransfusion of red cell-rich blood is known to follow i.v. injection of adrenaline in dogs (Kramer and Luft, 1951; Donald and Aarhus, 1974). Alternatively, this increase in Hb may have resulted from either increased sodium and water excretion by the kidneys (Meyer, McNay and Goldberg, 1967; Schoeppe, 1977) or the redistribution of extra-cellular fluid. The prompt return to control values after stopping the infusion of dopamine would seem to make the first explanation the most likely hypothesis. This increase in haemoglobin concentration has not been reported previously during infusions of dopamine, but was responsible for a major part of the increase in oxygen availability which occurred.

Changes during dopamine infusion

During the second 30 min of infusion of dopamine the mean cardiac output decreased to initial control values or less in both groups. This may have resulted from either a change in ventricular preload or a change in myocardial inotropy. With the small dose, a decrease in cardiac output of at least 30% of the control value occurred during the second 30 min of infusion in five of the six dogs in which cardiac output had initially increased. During the same period only very small changes in pulmonary capillary wedge pressure were recorded. This suggests that the initial increase in inotropy may not have been sustained throughout the duration of the infusion.

Changes after cessation of dopamine

In both dose groups, cessation of the infusion resulted in significant ($P < 0.05$) reductions in cardiac output, $P\bar{v}_{O_2}$, Ca_{O_2} and oxygen availability. The reduction in $\dot{Q}s/\dot{Q}t$ which occurred at this time may be attributable to the simultaneous decrease in cardiac output (Smith, Cheney and Winter, 1974). In the large-dose group, heart rate, haemoglobin concentration and mean pulmonary artery pressure decreased significantly also. These results suggest that dependence on infusions of dopamine may develop rapidly even when there is no cardiac dysfunction. In both groups oxygen consumption and carbon dioxide output had not returned to control 1 h after discontinuing the dopamine. Thus during withdrawal of the drug oxygen transport is depressed and metabolic demand is high. Data on other catecholamines during the withdrawal period are not available, but the necessity for "weaning" from infusions of catecholamines is well recognized clinically.

In conclusion, dopamine not only increased oxygen delivery to the systemic circulation but it also increased overall oxygen utilization. Dopamine 10 $\mu g\ kg^{-1}\ min^{-1}$ resulted in a larger increase in oxygen availability and a smaller increase in oxygen consumption than did a dose of 30 $\mu g\ kg^{-1}\ min^{-1}$. Because dopamine increases cardiac contractility and therefore cardiac output by an indirect effect in addition to a direct beta-agonist effect (Lumley, Broadley and Levy, 1977) it may be expected that the dose–response curve for changes in oxygen delivery will lie to the left of that for changes in oxygen utilization. As a consequence, doses in excess of those required to produce peak oxygen delivery will only increase oxygen consumption and could adversely affect the balance of oxygen transport.

When both doses of dopamine were withdrawn the immediate decrease in oxygen availability was not matched by a similar decrease in oxygen utilization. This imbalance may be an important factor in determining the rate at which dopamine should be withdrawn after it has been administered for the treatment of heart failure.

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TRANSPORT DE L'OXYGENE PENDANT L'INFUSION DE DOPAMINE A DES CHIENS

RESUME

Les cathécholamines augmentent non seulement le débit d'oxygène aux tissus, mais aussi la consommation d'oxygène. L'effet d'une infusion de chlorhydrate de dopamine a été étudié à deux doses, sur six chiens. La dopamine administrée à raison de 10 μg kg^{-1} min^{-1} a provoqué une augmentation de la concentration d'hémoglobine et modifié le débit cardiaque, la disponibilité en oxygène et la consommation totale d'oxygène du corps, de telle sorte que le rapport disponibilité en oxygène a augmenté et que la ($Ca_{O_2} - C\bar{v}_{O_2}$) a diminué, bien que ces changements n'aient pas atteint une ampleur ayant une signification statistique. La dopamine administrée à raison de 30 μg kg^{-1} min^{-1} ($P < 0,05$)

a augmenté la fréquence cardiaque, la concentration d'hémoglobine et le Ca_{O_2} tout en réduisant d'une manière significative le volume systolique et la V_D/V_T. Bien que la disponibilité en oxygène ait augmenté, l'augmentation de la consommation d'oxygène a été plus forte n'entraînant qu'une réduction insignifiante du point de vue statistique, du rapport de la disponibilité en oxygène et de l'augmentation de la ($Ca_{O_2}-C\bar{v}_{O_2}$). L'arrêt de l'infusion de dopamine a été suivi d'une diminution importante ($P<0{,}05$) du débit cardiaque, du $P\bar{v}_{O_2}$, du Ca_{O_2} et de la disponibilité en oxygène, ainsi que de la consommation d'oxygène et d'une augmentation dans la ($Ca_{O_2}-C\bar{v}_{O_2}$). On en a conclu que la débit maximal d'oxygène a lieu à une dose plus faible que celle requise pour produire l'augmentation maximale de la consommation d'oxygène.

SAUERSTOFFTRANSPORT WÄHREND DOPAMIN-INFUSION BEI HUNDEN

ZUSAMMENFASSUNG

Katecholamine erhöhen nicht nur den Sauerstofftransport zu den Geweben, sondern auch den Sauerstoffverbrauch. Eine Infusion von Dopamin Hydrochlorid in zwei Dosen wurde an sechs Hunden studiert. 10 $\mu g\ kg^{-1}\ min^{-1}$ Dopamin bewirkte eine erhöhte Hämoglobinkonzentration und veränderte das Herzminutenvolumen, die Sauerstoffverfugbarkeit und den Sauerstoffgesamtverbrauch so, dass das Sauerstoff-Verfugbarkeitsverhältnis anstieg und ($Ca_{O_2}-C\bar{v}_{O_2}$) sank, wenn auch diese Veränderungen statistisch gesehen nicht wesentlich waren. Eine Dosis von 30 $\mu g\ kg^{-1}\ min^{-1}$ Dopamin ($P<0{,}05$) erhöhte das Herzminutenvolumen, die Hämoglobinkonzentration und Ca_{O_2}, und senkte wesentlich das Schlagvolumen und V_D/V_T. Obwohl die Sauerstoffverfügbarkeit stieg, waren die Anstiege des Sauerstoffverbrauches grösser, was zu statistisch unwesentlichen Abstiegen des Sauerstoffverfügbarkeitsverhältnisses und zu einem Anstieg von ($Ca_{O_2}-C\bar{v}_{O_2}$) führte. Beendigung der Dopamin-Infusion führte zu wesentlichen ($P<0{,}05$) Abstiegen von Herzminutenvolumen, $P\bar{v}_{O_2}$, Ca_{O_2}, Sauerstoffverfügbarkeit und -verbrauch, sowie zum Anstieg von ($Ca_{O_2}-C\bar{v}_{O_2}$). Man schloss, dass die maximale Sauerstoffabgabe bei einer niedrigeren Dosis als der erfolgt, die zur Hervorrufung des Maximalanstieges des Sauerstoffverbrauches erforderlich ist.

TRANSPORTE DE OXIGENO DURANTE INFUSION DE DOPAMINA EN PERROS

SUMARIO

Las catecolaminas aumentan no sólo el aporte de oxígeno a los tejidos sino también el consumo del mismo (V_{O_2}). Se estudió el efecto de una infusión de hipocloruro de dopamina en dos dosis, cada una de ellas administrada a seis perros. Con 10 $\mu g\ kg^{-1}\ min^{-1}$ de dopamina, ocurrió un aumento de la concentración de hemoglobina y una alteración del volumen-minuto, de la disponibilidad de oxígeno y del consumo corporal total del mismo, a tal punto que aumentara la relación de disponibilidad de oxígeno y disminuyera el ($Ca_{O_2}-C\bar{v}_{O_2}$), aunque esas modificaciones no fueran significativas desde el punto de vista estadístico. Con 30 $\mu g\ kg^{-1}\ min^{-1}$ de dopamina, se registró un aumento del ritmo cárdiaco ($P<0{,}05$), de la concentración de hemoglobina y del Ca_{O_2} así como una disminución significativa de la descarga sistólica y del V_D/V_T. Aunque aumentara la disponibilidad de oxígeno, los aumentos en el consumo del mismo la sobre pasaron y resultaron en una disminución de la relación de disponibilidad de oxígeno estadísticamente insignificante y en un aumento del ($Ca_{O_2}-C\bar{v}_{O_2}$). Al poner término a la infusión de dopamina, se registraron reducciones significatives del volumen-minuto ($P<0{,}05$), del $P\bar{v}_{O_2}$, del Ca_{O_2}, de la disponibilidad de oxígeno y de su consumo y un aumento del ($Ca_{O_2}-C\bar{v}_{O_2}$). Se llegó a la conclusión de que el aporte máximo de oxígeno se produce con una dosis menor que la necesaria para provocar el aumento máximo del consumo de oxígeno.

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METABOLIC CHANGES DURING DOPAMINE INFUSION IN DOGS

G. M. HALL, C. YOUNG AND A. SCOTT

SUMMARY

The effects were investigated, in 12 dogs, of the infusion of dopamine 10 or 30 μg kg^{-1} min^{-1} on circulating glucose, glycerol, lactate and potassium concentrations. Both doses of dopamine produced an initial increase in blood glucose concentration ($P < 0.05$) followed by hypoglycaemia ($P < 0.05$). Lipolysis was stimulated as shown by an increase in plasma glycerol concentrations with dopamine 10 μg kg^{-1} min^{-1} ($P < 0.05$) and dopamine 30 μg kg^{-1} min^{-1} ($P < 0.01$). Blood lactate concentrations increased slightly in both groups, but this was significant ($P < 0.05$) only in the dogs infused with dopamine 10 μg kg^{-1} min^{-1}. Dopamine had no significant effect on the plasma potassium concentration.

It is well known that the inotropic agents adrenaline, noradrenaline and isoprenaline stimulate various aspects of metabolism (Himms-Hagen, 1967). Recent studies have shown also that salbutamol, administered i.v. in small doses to produce bronchodilatation, has significant metabolic activity (Neville et al., 1977). Goldberg (1977) claimed that dopamine has less effect on metabolism than adrenaline or isoprenaline, although no evidence was given to support this contention.

In this study we have examined the effects of the infusion in dogs of dopamine 10 and 30 μg kg^{-1} min^{-1} on circulating glucose, glycerol, lactate and potassium concentrations.

Such information is relevant to the management of patients receiving dopamine infusions, and is also of value in attempting to define the adrenoreceptor agonist activity of dopamine.

METHODS

The details of the anaesthetic technique and surgical preparation of the dogs, and the experimental procedure for the infusion of dopamine 10 and 30 μg kg^{-1} min^{-1}, have been described in detail in the previous paper (Scott, Chakrabarti and Hall, 1979). Central venous blood samples were analysed in duplicate for blood glucose (Werner, Rey and Wielinger, 1970), plasma glycerol (Eggstein and Kuhlmann, 1974), blood lactate (Hohorst, 1962) and plasma potassium concentrations (flame photometry). The results from the sample collected after 30 min of the initial saline infusion were used as the control values and statistical analysis of the results was undertaken as described previously (Scott, Chakrabarti and Hall, 1979).

RESULTS

The infusion of dopamine both 10 and 30 μg kg^{-1} min^{-1} produced a biphasic change in blood glucose concentration (fig. 1). There was an initial increase in glucose values after 45 min ($P < 0.05$) followed by a decrease to control values. During the subsequent saline infusion, the glucose was decreased significantly ($P < 0.05$) below control values.

Dopamine 10 μg kg^{-1} min^{-1} produced a significant increase ($P < 0.05$) in plasma glycerol concentration after 60, 75 and 90 min (fig. 2). There was an even greater response to dopamine 30 μg kg^{-1} min^{-1}, with a three-fold increase in glycerol concentration after 60 min ($P < 0.01$). Furthermore, the stimulation of lipolysis with the larger dose of dopamine persisted into the second period of saline infusion, so that there was still a significant increase ($P < 0.05$) in plasma glycerol concentration 45 min after the dopamine was discontinued.

Blood lactate concentration increased slightly with both doses of dopamine (fig. 3), but this was statistically significant ($P < 0.05$) only with dopamine 10 μg kg^{-1} min^{-1} in the latter half of the period of infusion of catecholamine.

Plasma potassium concentration decreased by only 0.25 mmol litre^{-1} during the infusion of the small dose of dopamine and 0.5 mmol litre^{-1} with 30 μg kg^{-1} min^{-1} (fig. 4). Neither change was statistically significant.

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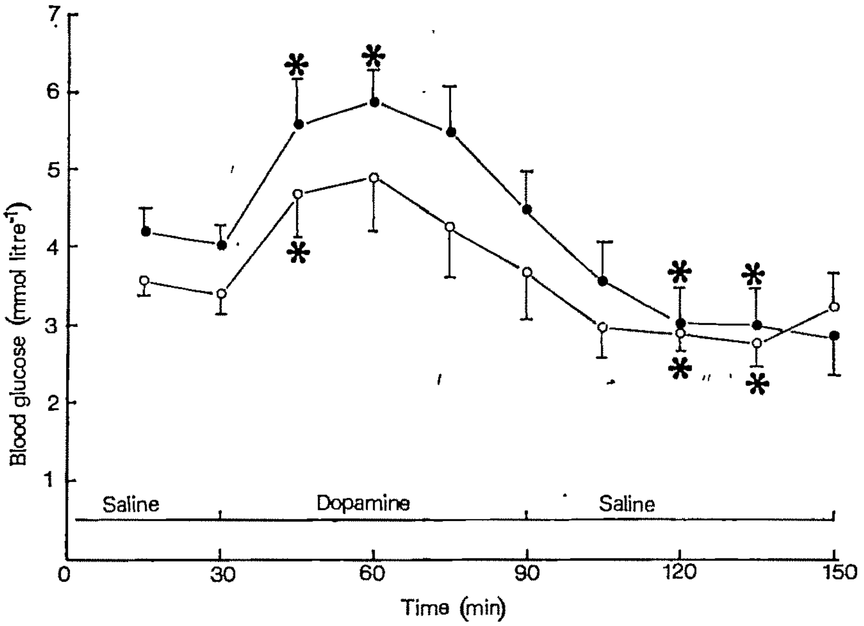

FIG. 1. Mean (± SEM) blood glucose concentration (mmol litre^{-1}) in dogs infused with dopamine 30 μg kg^{-1} min^{-1} (closed circles) and dopamine 10 μg kg^{-1} min^{-1} (open circles). $*P < 0.05$ compared with 30-min sample.

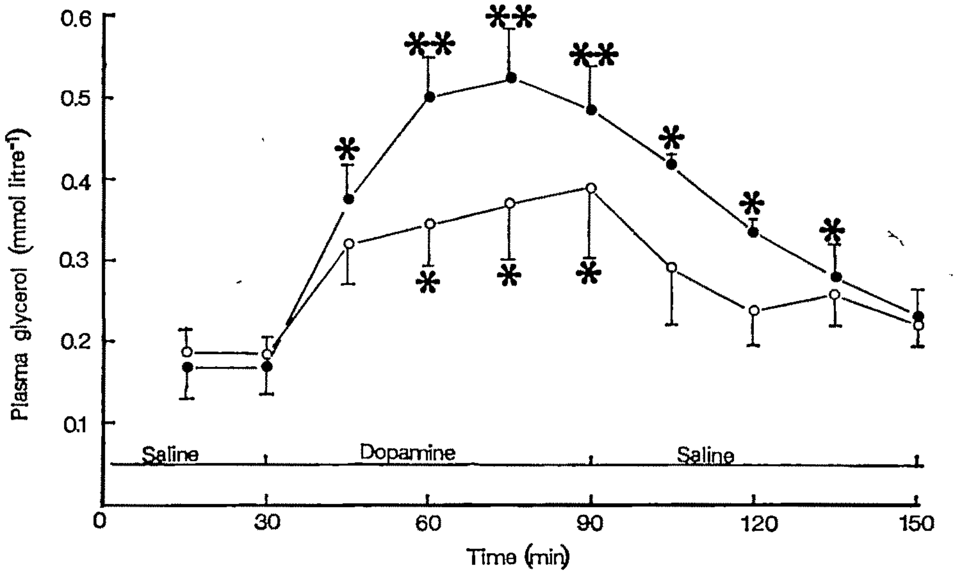

FIG. 2. Mean (± SEM) plasma glycerol concentration (mmol litre^{-1}) in dogs infused with dopamine 30 μg kg^{-1} min^{-1} (closed circles) and dopamine 10 μg kg^{-1} min^{-1} (open circles). $*P < 0.05$; $**P < 0.01$ compared with 30-min sample.

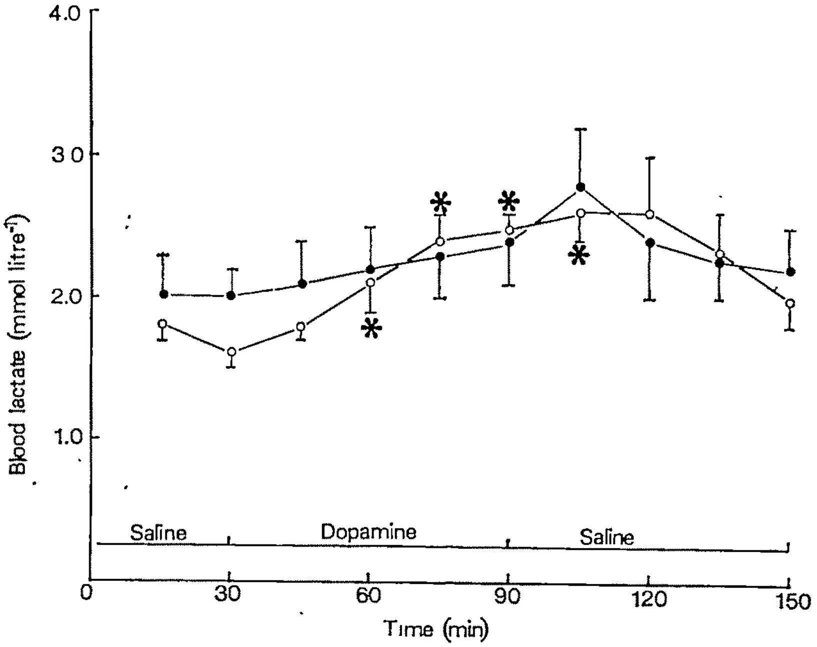

FIG. 3. Mean (±SEM) blood lactate concentration (mmol litre^{-1}) in dogs infused with dopamine 30 μg kg^{-1} min^{-1} (closed circles) and dopamine 10 μg kg^{-1} min^{-1} (open circles). *$P < 0.05$ compared with 30-min sample.

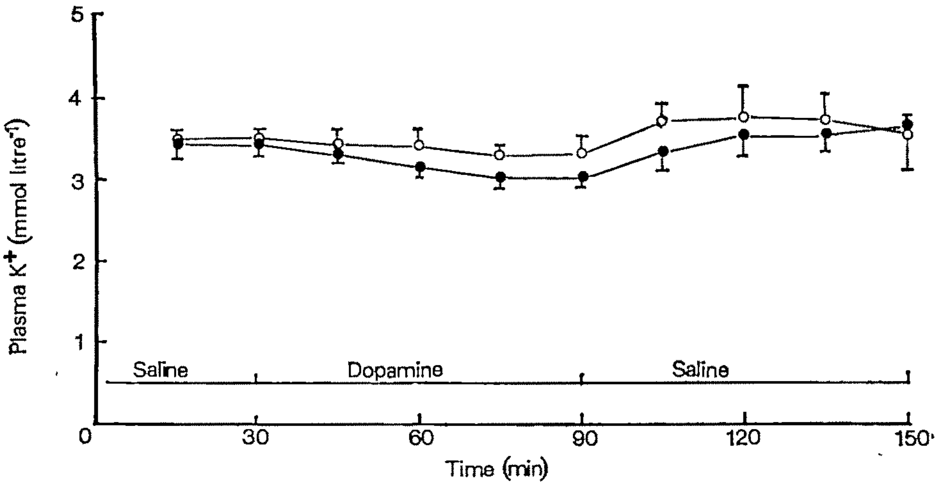

FIG. 4. Mean (±SEM) plasma potassium concentration (mmol litre^{-1}) in dogs infused with dopamine 30 μg kg^{-1} min^{-1} (closed circles) and dopamine 10 μg kg^{-1} min^{-1} (open circles).

DISCUSSION

The biphasic response of the blood glucose concentration to infusion of dopamine (fig. 1) has not been reported previously. Leblanc and others (1977) showed that, in man, the glycaemic response was not sustained when dopamine 4 μg kg^{-1} min^{-1} was infused i.v. for 2 h, but they failed to continue their observations after the dopamine was discontinued. However, their results suggested a possible mechanism for the biphasic response. Dopamine was found to stimulate a rapid but transient increase in glucagon secretion from the α cells of the pancreas, followed by a slower but more sustained secretion of insulin. Thus, the increase in blood glucose is probably caused by the effect of glucagon in stimulating hepatic glycogenolysis, although it is not possible to exclude a direct action of dopamine on glycogenolysis. The failure to sustain the hyperglycaemia and the occurrence of subsequent hypoglycaemia are the results of the persistent hyperinsulinaemia. Chideckel and others (1977) have suggested that the effect of catecholamines on hepatic glucose metabolism is always mediated indirectly via changes in secretion of pancreatic glucagon and insulin. This indirect effect of catecholamines may explain the difficulty in ascribing the stimulation of hepatic glycogenolysis to either α or β adrenoreceptors.

It is possible that the results obtained in the dog may not be applicable directly to man, but the results of Leblanc and others (1977) and our findings of unstable glucose values during infusions of dopamine (authors' unpublished observations) suggest that the biphasic glucose response has important clinical implications. We recommend that frequent monitoring of the blood glucose concentration is undertaken not only during the infusion of dopamine but also after the catecholamine is discontinued, to detect possible hypoglycaemia.

We chose to measure plasma glycerol rather than plasma free fatty acid (FFA) concentrations to indicate changes in fat metabolism, as we consider the former to be a more accurate indicator of lipolysis (Hall et al., 1978). The significant increase in lipolysis observed with both doses of dopamine (fig. 2) showed that the catecholamine was a potent stimulator of the adrenoreceptors in the adipose tissue. Fain (1973) has demonstrated that lipolysis is subserved by β_1-adrenoreceptors in all animal species, so that we would predict similar changes in man. Random estimations of plasma FFA values in the dogs confirmed the increase in lipolysis, and when dopamine 30 μg kg^{-1} min^{-1} was infused individual values greater than 2 mmol litre^{-1} were found. It is possible that high FFA values predispose to cardiac arrhythmias (Oliver, 1972), although this is disputed by most cardiologists (Opie, 1972). It is usually considered that the infusion of dopamine has little effect on heart rate or myocardial irritability, but recent studies by Chauve, Castro and Fontan (1977) and Miller (1977) have reported the occurrence of tachyarrhythmias. Although it has been assumed that this represents a direct effect of dopamine on the myocardium, a secondary effect from the stimulation of lipolysis may be contributory.

The cause of the statistically significant, but metabolically small, increase in lactate concentration observed with the administration of dopamine 10 μg kg^{-1} min^{-1} (fig. 3) is obscure, particularly as oxygen availability increased more than oxygen consumption (Scott, Chakrabarti and Hall, 1979). However, the failure of the larger dose of dopamine to increase blood lactate concentration significantly showed that there was unlikely to be an important contribution from the stimulation of β_2-adrenoreceptors responsible for lactate production in muscle (Brody and McNeill, 1970). Dopamine had little effect on plasma potassium concentration (fig. 4), but if the associated haemoconcentration was a result of a diuresis (Scott, Chakrabarti and Hall, 1979) this may prevent the full extent of the hypokalaemic response from being recorded.

We conclude that the administration of dopamine i.v. is associated with significant changes in glucose and fat metabolism. The stimulation of lipolysis shows that dopamine is an agonist for β_1-adrenoreceptors and this catecholamine appears to be unique in stimulating α, β_1 and dopaminergic receptors.

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CHANGEMENTS METABOLIQUES PENDANT L'INFUSION DE DOPAMINE A DES CHIENS

RESUME

On a étudié sur 12 chiens, les effets de l'infusion de dopamine, à raison de 10 et de 30 $\mu g\ kg^{-1}\ min^{-1}$, sur les concentrations de glucose, de glycérol, de lactate et de potassium dans la circulation. Ces deux doses de dopamine ont produit à l'origine une augmentation de la concentration de glucose dans le sang ($P < 0{,}05$) et celle-ci a été suivie d'une hypoglycémie ($P < 0{,}05$). La lipolyse a été stimulée, comme on a pu le voir par une augmentation des concentrations de glycérol dans le plasma, par de la dopamine à 10 $\mu g\ kg^{-1}\ min^{-1}$ ($P < 0{,}05$) et de la dopamine à 30 $\mu g\ kg^{-1}\ min^{-1}$ ($P < 0{,}01$). Les concentrations de lactate dans le sang ont augmenté légèrement dans chacun des deux groupes, mais cela n'a été significatif ($P < 0{,}05$) que chez les chiens soumis à une infusion ce 10 $\mu g\ kg^{-1}\ min^{-1}$. La dopamine n'a eu aucun effet sur les concentrations de potassium dans le plasma.

STOFFWECHSELÄNDERUNGEN WÄHREND DOPAMIN-INFUSION BEI HUNDEN

ZUSAMMENFASSUNG

Bei 12 Hunden wurden die Wirkungen einer Infusion von 10 oder 30 μg Dopamin auf zirkulierende Konzentrationen von Glukose, Glyzerol, Laktat und Kalium untersucht. Dopamin bewirkte einen anfanglichen Anstieg der Blut-Glukosekonzentration ($P < 0{,}05$), gefolgt von Hypoglykämie ($P < 0{,}05$). Lipolyse wurde stimuliert, wie durch einen Anstieg der Blut-Glyzerolkonzentrationen mit Dopamin 10 $\mu g\ kg^{-1}\ min^{-1}$ ($P < 0{,}05$) und Dopamin 30 $\mu g\ kg^{-1}\ min^{-1}$ ($P < 0{,}01$) gezeigt wurde. Blut-Laktatkonzentrationen stiegen leicht, doch war dies nur bei Hunden wesentlich ($P < 0{,}05$), die eine Infusion von 10 $\mu g\ kg^{-1}\ min^{-1}$ erhalten hatten. Auf die Plasma-Kalium-konzentrationen hatte Dopamin keinen Einfluss.

CAMBIOS METABOLICOS DURANTE LA INFUSION DE DOPAMINA EN PERROS

SUMARIO

En 12 perros, se averiguaron los efectos de la infusión de 10 y 30 $\mu g\ kg^{-1}\ min^{-1}$ de dopamina en las concentraciones circulantes de glucosa, glicerol, lactato y potasio. Ambas dosis de dopamina causaron un aumento inicial de la concentración de glucosa en la sangre ($P < 0{,}05$), seguido por hipoglicemia ($P < 0{,}05$). Se estimuló la lipólisis, tal como indicado por un aumento en las concentraciones de glicerol en el plasma, con 10 $\mu g\ kg^{-1}\ min^{-1}$ ($P < 0{,}05$) y 30 $\mu g\ kg^{-1}\ min^{-1}$ de dopamina ($P < 0{,}01$). Las concentraciones de lactato en la sangre aumentaron ligeramente en ambos grupos, pero fueron significantes únicamente ($P < 0{,}05$) en perros infusados con 10 $\mu g\ kg^{-1}\ min^{-1}$ de dopamina. La dopamina no tuvo ningún efecto significativo en la concentración de potasio en la sangre.

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DEPRESSION OF TRANSMITTER RELEASE AND POSTJUNCTIONAL SENSITIVITY DURING NEUROMUSCULAR BLOCK PRODUCED BY ANTIBIOTICS

Y. N. SINGH, I. G. MARSHALL AND A. L. HARVEY

SUMMARY

In an attempt to elucidate the mechanisms by which antibiotics induce muscle paralysis, the effects of streptomycin, lincomycin, polymyxin B and clindamycin were investigated in the mouse phrenic nerve–hemidiaphragm preparation. Streptomycin resembled magnesium in reducing miniature endplate potential (m.e.p.p.) amplitude and frequency, whereas lincomycin, clindamycin and polymyxin B resembled tubocurarine in abolishing m.e.p.p. Endplate potential (e.p.p.) quantal content in streptomycin was 9, similar to that found in magnesium (5), whereas quantal contents in lincomycin (42), polymyxin B (37) and clindamycin (32) lay between values found in magnesium and in tubocurarine (123). Control quantal content was 152. In the presence of a mixture of magnesium and tubocurarine, no m.e.p.p. could be recorded and quantal content was 39. Blockade of twitches by a mixture of magnesium and tubocurarine was more successfully reversed by a mixture of calcium and neostigmine (to 70% of control) than by either calcium (to 49% of control) or by neostigmine (to 30% of control) alone. Lincomycin- and polymyxin B-induced blockades were poorly reversed by a mixture of the two reversal agents. It is concluded that streptomycin has a magnesium-like action whereas lincomycin, clindamycin and polymyxin B have relatively greater postjunctional and less prejunctional blocking activities. However, the effects of lincomycin and polymyxin B were not analogous to those of a tubocurarine–magnesium mixture, and their mechanism of action is still unclear. Clindamycin produced effects compatible with local anaesthetic activity.

Several classes of antibiotics, particularly the aminoglycosides (e.g. streptomycin, neomycin, kanamycin), tetracyclines, polymyxins, and lincomycin and clindamycin have been shown to produce skeletal muscle paralysis both in man and in experimental animals (Pittinger, Eryasa and Adamson, 1970; Pittinger and Adamson, 1972; Fogdall and Miller, 1974). The muscle paralysis produced by the aminoglycosides has been studied extensively both *in vivo* and *in vitro* and it has been proposed that the predominant mechanism of action is a magnesium-like depression of the evoked release of acetylcholine (Elmqvist and Josefsson, 1962; Vital Brazil and Prado-Franceschi, 1969; Wright and Collier, 1977; Singh, Harvey and Marshall, 1978; Singh, Marshall and Harvey, 1978), but there is evidence also of a component of postjunctional blocking activity (Vital Brazil and Corrado, 1957; Elmqvist and Josefsson, 1962; Singh, Harvey and Marshall, 1978; Singh, Marshall and Harvey, 1978). The neuromuscular block produced by the aminoglycosides is reversed by calcium ions, suggesting that the aminoglycosides block transmitter release by inhibiting the influx of calcium ions into nerve terminals on nerve stimulation (Corrado, Ramos and de Escobar, 1959; Adams et al., 1976; Singh, Harvey and Marshall, 1978; Singh, Marshall and Harvey, 1978). The actions of the other classes of antibiotics that produce muscle paralysis have not been studied to the same extent as those of the aminoglycosides.

The site of action of several antibiotics (streptomycin, lincomycin, clindamycin and polymyxin B) has been investigated now by means of intracellular recording techniques. In these electrophysiological experiments, prejunctional actions were indicated by effects on the quantal content of endplate potentials (e.p.p.), which is a measure of the amount of acetylcholine released by a single nerve impulse. Changes in the frequency of the spontaneously-occurring miniature endplate potentials (m.e.p.p.) were taken also to indicate prejunctional actions. Postjunctional effects were indicated by effects on the amplitude of m.e.p.p. Thus, the results provide information on the effects of the antibiotics on transmitter release and on postjunctional receptor sensitivity. The antibiotics tested were compared with magnesium and with

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tubocurarine as examples of drugs acting by predominantly prejunctional and postjunctional mechanisms respectively, and with a combination of magnesium and tubocurarine as a type of mixed pre- and postsynaptic blocking activity. Since the effects of lincomycin and of polymyxin B in the electrophysiological studies resembled those of a tubocurarine–magnesium mixture, the reversibility of the twitch depression produced by lincomycin and polymyxin B has been re-investigated using combinations of calcium and neostigmine.

METHODS

All experiments were performed on phrenic nerve–hemidiaphragm preparations from mice (Porton strain, 20–35 g).

Intracellular recording

Nerve–muscle preparations were pinned to the base of a 15-ml tissue bath through which Krebs–Henseleit (Krebs and Henseleit, 1932) solution was passed at a rate of 2.5–3 ml min^{-1}. The solution had previously been gassed with oxygen containing 5% carbon dioxide and was maintained at 30–32 °C.

The tissue bath was mounted on the stage of a binocular microscope (American Optics or Zeiss Jena Ergaval) fitted with a Leitz UM20/0.33 long-working-distance objective giving a magnification of approximately 300 times. E.p.p. and m.e.p.p. and membrane potentials were recorded with 2 mol $litre^{-1}$ potassium acetate-filled glass capillary microelectrodes (5–15 MΩ resistance). Signals were amplified by a WPI M701 electrometer and displayed simultaneously on Tektronix 5102 and 5103 oscilloscopes. The signals were recorded continuously on 35-mm film by a Grass oscilloscope camera. Single events were photographed from a storage oscilloscope on Polaroid film. Records were magnified by a film viewer and measured manually.

The endplate regions were localized by following nerve twigs and penetrating muscle fibres until spontaneous miniature endplate potentials (m.e.p.p.) with fast rise times (less than 1 ms) could be recorded. Control recordings of m.e.p.p. were made for at least 5 min from six different endplate regions before the administration of a drug.

The Krebs–Henseleit solution was replaced by an identical solution containing the antibiotic under study. The concentrations of antibiotics were chosen to produce abolition of twitching in response to nerve stimulation in 30–85 min. Once responses to nerve stimulation were below the threshold for muscle contraction, several endplate regions were impaled and endplate potentials (e.p.p.) in response to nerve stimulation (0.2-ms pulses, 0.5 Hz frequency) and spontaneous m.e.p.p. were recorded.

To enable comparison between endplate regions with different resting membrane potentials e.p.p. and m.e.p.p. amplitudes were converted to a standard membrane potential of −70 mV and e.p.p. were corrected for non-linear summation (Hubbard, Llinas and Quastel, 1969). In each experimental situation, the intracellular recordings were obtained from six fibres in each muscle preparation. These values were averaged to produce a mean value for the muscle preparation. The mean values from six muscle preparations were then averaged to produce the quantal content values quoted in the table and text.

To obtain a measure of e.p.p. quantal content in the absence of drugs, muscles were immobilized by cutting the muscle fibres 1–2 mm on each side of the central band of endplate regions (Barstad and Lilleheil, 1968). E.p.p. quantal content was measured from responses to trains of impulses (70 Hz for 0.75 s). Under these conditions e.p.p. amplitude decreased during the first few impulses of the train and then was maintained at a fairly constant value. The quantal content of the last 30 e.p.p. in the train was calculated by the method of variance (del Castillo and Katz, 1954) and the quantal content of the first e.p.p. was then obtained by proportionality. In these experiments e.p.p. amplitudes were corrected to a standard membrane potential of −40 mV and were corrected for non-linear summation.

Twitch tension experiments

For twitch tension studies, mouse phrenic nerve–hemidiaphragm preparations were mounted in Krebs–Henseleit solution maintained at 32 °C and gassed with oxygen containing carbon dioxide (5%). Resting tension was approximately 0.5 g and contractions were recorded isometrically by Grass FTO3C force-displacement transducers connected to a Grass 7 polygraph. Blocking drugs were added for about 5–10 min to preparations that were stimulated via the phrenic nerve at a frequency of 0.1 Hz with rectangular pulses of 0.2 ms duration and of a strength greater than that necessary to elicit maximal twitches. To assess reversibility of muscle paralysis an 80–90% block was established and mixtures of calcium chloride to a final calcium concentration of 5 mmol $litre^{-1}$ or 10 mmol $litre^{-1}$ and neostigmine 1 μg ml^{-1} (3 μmol $litre^{-1}$) were added. The extent of reversal was measured 5 min after addition of the reversal mixture and the recovery values expressed as percentages of the control twitch height. All results quoted in the text and table, represent mean ± standard error of six observations. Differences between means were analysed by non-paired Student's t test or by the Mann–Whitney U test. Values of $P < 0.05$ were regarded as statistically significant.

Drugs

Drugs used were tubocurarine chloride, streptomycin sulphate (both Sigma); polymyxin B sulphate (Wellcome), lincomycin hydrochloride and clindamycin hydrochloride (Upjohn).

RESULTS

Intracellular recording

In preparations in which muscle contraction in response to nerve stimulation was inhibited by tubocurarine 5 μmol litre^{-1} no m.e.p.p. could be recorded. E.p.p. varied only slightly in amplitude (fig. 1) and the e.p.p. quantal content of 123 ± 10 calculated by analysis of variance was not significantly different from the quantal content of 152 ± 17 obtained in the absence of drugs for the first e.p.p. in the train in cut hemidiaphragms.

In preparations paralysed by magnesium 19 mmol litre^{-1}, m.e.p.p. could still be recorded (fig. 2) although m.e.p.p. amplitude was 33 ± 7% lower than in control preparations (table I). E.p.p. amplitude fluctuated randomly with occasional failures (fig. 1). Quantal content of e.p.p. calculated by analysis of variance was 5 ± 0.5. Neither tubocurarine nor magnesium produced any significant change in membrane potential.

At the concentrations tested, streptomycin, polymyxin B, lincomycin and clindamycin did not change membrane potential (table I).

In preparations paralysed by streptomycin 1.23 mmol litre^{-1} m.e.p.p. of a reduced amplitude (56 ± 8% lower than control) could be recorded (fig. 2, table I). As observed in magnesium-paralysed preparations, e.p.p. fluctuated randomly in amplitude, with some failures (fig. 1). Quantal content of e.p.p. in the presence of streptomycin 1.23 mmol litre^{-1} was 9 ± 0.8.

After neuromuscular block produced by polymyxin B 0.085 mmol litre^{-1}, lincomycin 4 mmol litre^{-1} or clindamycin 0.7 mmol litre^{-1} it was impossible to record m.e.p.p. The variation of e.p.p. amplitude was intermediate between that in tubocurarine and that in magnesium (fig. 1). E.p.p. quantal contents in the presence of these three antibiotics ranged from 32 to 42 (table I). A similar pattern was observed in preparations blocked by a mixture of postjunctionally-active and prejunctionally-active agents, that is tubocurarine 1.7 μmol litre^{-1} and magnesium 7 mmol litre^{-1}. In the presence of this mixture of agents, no m.e.p.p. could be recorded and e.p.p. quantal content was 39 ± 5. However, in preparations blocked with clindamycin 0.7 mmol litre^{-1}, e.p.p. could be recorded in only some of the endplates penetrated. When endplates were penetrated before abolition of twitching, very small m.e.p.p. (around 15% of control amplitude) were recorded. M.e.p.p. frequency was increased to around 15 s^{-1} at this time. Thus, streptomycin appears to act mainly prejunctionally, whereas polymyxin B, lincomycin and clindamycin have mixed pre- and postjunctional blocking effects.

TABLE I. *M.e.p.p. amplitude, m.e.p.p. frequency, e.p.p. quantal content and membrane potential from endplates paralysed by antibiotics, magnesium and tubocurarine.* †*Significantly different* ($P < 0.05$) *from control;* **significantly different* ($P < 0.05$) *from control and tubocurarine;* ‡*significantly different* ($P < 0.05$) *from magnesium and streptomycin;* §*obtained from cut muscle preparations;* ¶*concn in μmol litre*$^{-1}$

Treatment	Drug concn to produce neuromusc. block (mmol litre^{-1})¶	M.e.p.p.		E.p.p. (mean quantal content)	Membrane potential (mV)
		Amplitude (mV)	Frequency (Hz)		
Control	—	1.02 ± 0.03	1.50 ± 0.14	152 ± 17§	72.9 ± 1.5
Tubocurarine	5¶	0†‡	0†‡	123 ± 10	73.7 ± 1.8
Magnesium	19	0.67 ± 0.06†	0.50 ± 0.05†	5 ± 0.5*	70.5 ± 1.1
Tubocurarine + magnesium	1.7¶ 7	0†	0†	39 ± 5*	72.2 ± 1.9
Streptomycin	1.23	0.44 ± 0.08†	0.60 ± 0.08†	9 ± 0.8*	71.8 ± 0.3
Polymyxin B	0.085	0†‡	0†‡	37 ± 4‡*	75.5 ± 2.8
Lincomycin	4	0†‡	0†‡	42 ± 5‡*	71.6 ± 1.1
Clindamycin	0.7	0†‡	0†‡	32 ± 8‡*	71.4 ± 2.0

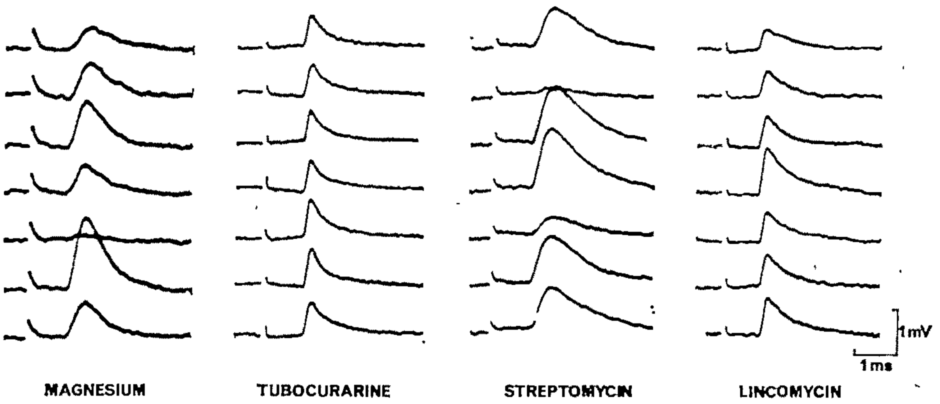

FIG. 1. Endplate potentials recorded intracellularly from mouse phrenic nerve–hemidiaphragm preparations after treatment with magnesium 19 mmol litre^{-1}, tubocurarine 5 μmol litre^{-1}, streptomycin 1.23 mmol litre^{-1} and lincomycin 4 mmol litre^{-1}. In each instance seven successive oscilloscope sweeps are represented. Note the variation in the height of e.p.p. recorded in magnesium whereas, in the presence of tubocurarine, e.p.p. amplitude did not vary markedly. The recordings in streptomycin were similar to those made in the presence of magnesium, whereas those in lincomycin were intermediate between recordings in magnesium and tubocurarine.

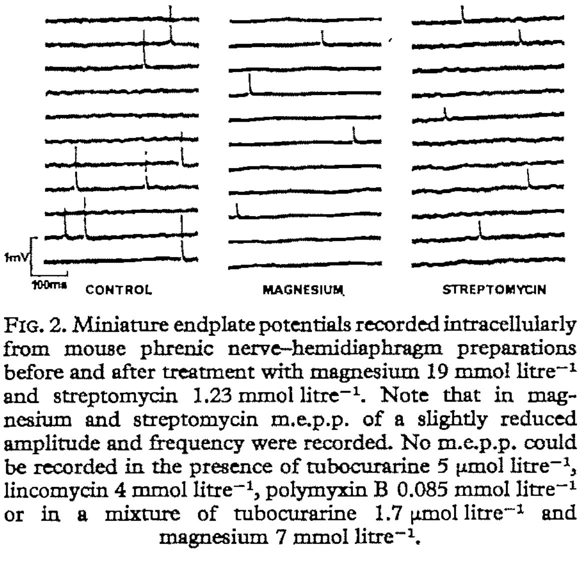

FIG. 2. Miniature endplate potentials recorded intracellularly from mouse phrenic nerve–hemidiaphragm preparations before and after treatment with magnesium 19 mmol litre^{-1} and streptomycin 1.23 mmol litre^{-1}. Note that in magnesium and streptomycin m.e.p.p. of a slightly reduced amplitude and frequency were recorded. No m.e.p.p. could be recorded in the presence of tubocurarine 5 μmol litre^{-1}, lincomycin 4 mmol litre^{-1}, polymyxin B 0.085 mmol litre^{-1} or in a mixture of tubocurarine 1.7 μmol litre^{-1} and magnesium 7 mmol litre^{-1}.

Twitch tension studies

Results from intracellular recording studies indicated that lincomycin and polymyxin B produced effects quantitatively similar to the effect of a mixture of tubocurarine and magnesium. Tubocurarine blockade is reversed by neostigmine but not by calcium, and magnesium blockade is reversed by calcium but not by neostigmine, whereas the blockades produced by lincomycin and by polymyxin B were poorly reversible by calcium and neostigmine (Singh, Harvey and Marshall, 1978). We have now studied the ability of a combination of neostigmine and calcium to reverse neuromuscular blockades produced by lincomycin, polymyxin B and a mixture of tubocurarine and magnesium.

A mixture of tubocurarine 2 μmol litre^{-1} and magnesium 8 mmol litre^{-1} reduced twitch height to 11–16% of control size in about 5–10 min. The resultant block was reversed to 30±5% of control by doubling the calcium concentration of the bathing medium to 5 mmol litre^{-1} and to 49±6% of control by neostigmine 3 μmol litre^{-1}. However, the block was reversed to 70±5% of control by a mixture of calcium 5 mmol litre^{-1} and neostigmine 3 μmol litre^{-1}. Lincomycin-induced block (2.6 mmol litre^{-1}) was reversed to 25±1% of control by the mixture of calcium and neostigmine. Since calcium 5 mmol litre^{-1} is almost totally ineffective against blockade induced by polymyxin B 0.3 mmol litre^{-1} (Singh, Harvey and Marshall, 1978), a mixture of calcium 10 mmol litre^{-1} and neostigmine 3 μmol litre^{-1} was tested. Although this mixture reversed polymyxin-induced block (0.3 mmol litre^{-1}) to only 31±5% of control, the reversal was poorly sustained, the block being re-established in 5–10 min.

DISCUSSION

Streptomycin, polymyxin B, lincomycin and clindamycin were compared with tubocurarine and magnesium as examples of reversible drugs acting predominantly to block postjunctional acetylcholine receptors and prejunctional release of acetylcholine respectively. Thus, in preparations blocked by tubocurarine the quantal content of e.p.p. was great, indicating that tubocurarine had little effect on the amount of acetylcholine released by nerve impulses. In these preparations m.e.p.p. amplitude was reduced to zero, demonstrating the postjunctional blocking action of tubocurarine. In contrast, in preparations blocked by magnesium the quantal content of e.p.p. was very low and the frequency of m.e.p.p. was reduced; these findings indicate prejunctional actions of magnesium. Additionally, magnesium has some postjunctional blocking actions, as revealed by the reduction in m.e.p.p. amplitude.

As shown previously by other workers (Vital Brazil and Corrado, 1957), we have demonstrated that neuromuscular block produced by the aminoglycoside antibiotic streptomycin, like that produced by magnesium, was associated with depression of both evoked and spontaneous acetylcholine release and reduced postjunctional sensitivity. Small quantal contents have also been measured in the presence of other aminoglycoside antibiotics including neomycin (Elmqvist and Josefsson, 1962) and amikacin (Singh, Marshall and Harvey, 1978), and the aminoglycoside-like antibiotic spectinomycin (Singh, Marshall and Harvey, 1979).

Quantal contents in the presence of polymyxin B, lincomycin and clindamycin were lower than control values, indicating that reduction of transmitter output is a component of the compounds' actions. The depression of quantal content, however, was not as marked as the reduction seen in the presence of magnesium or streptomycin. Since m.e.p.p. activity was abolished, it can be concluded that polymyxin B, lincomycin and clindamycin also have postjunctional blocking effects. Our results demonstrate that polymyxin B, lincomycin and clindamycin have more prejunctional blocking activity than tubocurarine. Since tubocurarine has prejunctional blocking effects during repetitive nerve stimulation (Miyamoto, 1978) it is possible that the prejunctional effects of these three antibiotics will predominate during normal voluntary movement when the pattern of nerve impulses to skeletal muscle more closely resembles repetitive stimulation than low-frequency single shock stimulation.

A mixture of tubocurarine and magnesium possessed effects quantitatively similar to those of polymyxin B, lincomycin and clindamycin on e.p.p. quantal content and m.e.p.p., but the blockade of twitches produced by the tubocurarine–magnesium mixture was reversed by a mixture of calcium and neostigmine whereas lincomycin- and polymyxin B-induced blockades were not reversed by calcium plus neostigmine. Thus, despite the superficial similarity of the effects of polymyxin B and of lincomycin to those of a magnesium–tubocurarine mixture, the mechanism of action of the antibiotics is not a simple combination of calcium- and anticholinesterase-reversible actions. Furthermore, although the effects of lincomycin and of polymyxin B on transmitter release and on postjunctional sensitivity are similar, the evidence presented is not sufficient to indicate that the two compounds share the same mechanisms. In fact, our previous studies have shown that concentrations of polymyxin B only slightly greater than those selectively blocking neuromuscular transmission have a depressant action on skeletal muscle contractility but no similar effect is seen with lincomycin (Singh, Harvey and Marshall, 1978).

The absence of e.p.p. activity immediately after muscle twitching was abolished by clindamycin probably indicates that the nerve terminals are no longer capable of conducting action potentials in the presence of the drug. A local anaesthetic activity of clindamycin has been described previously (Wright and Collier, 1976). The mixture of pre- and postjunctional blocking actions discussed above would be expected to contribute, along with the local anaesthetic action, to the muscle paralysing action of clindamycin. The increase in m.e.p.p. frequency before the abolition of m.e.p.p. activity has also been noted by Rubbo, Gergis and Sokoll (1977), but we have not analysed this effect in detail.

Our present results confirm that the aminoglycoside streptomycin acts primarily by a calcium-reversible prejunctional mechanism, whereas the other antibiotics tested act by different mechanisms. As the nature of the components of mixed pre- and postjunctional block produced by polymyxin B, lincomycin and clindamycin are as yet unknown, reversibility of these antibiotics by standard reversal agents remains difficult to predict and in the clinical situation it may be preferable to continue artificial ventilation until the return of spontaneous respiration.

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DEPRESSION DE LA SENSITIVITE POST-JONCTION ET DU DEGAGEMENT TRANSMETTEUR PENDANT LES BLOCAGES NEUROMUSCULAIRES PRODUITS PAR LES ANTIBIOTIQUES

RESUME

Au cours d'un essai qui a été fait pour élucider les mécanismes par lesquels les antibiotiques provoquent une paralysie des muscles, on a tout particulièrement étudié les effets de la streptomycine, de la lincomycine, de la polymyxine B et de la clindamycine sur une préparation nerf phrénique–demi-diaphragme d'une souris. La streptomycine a ressemblé au magnésium en réduisant l'amplitude et la fréquence du potentiel d'une plaque d'extrémité miniature (m.e.p.p.), alors que la lincomycine, la clindamycine et la polymyxine B ont ressemblé à la tubocurarine en abolissant le m.e.p.p. La teneur en quanta du potentiel de la plaque d'extrémité (e.p.p.) pour la streptomycine a été de 9, c'est-à-dire une valeur similaire à celle que l'on trouve dans le magnésium (5), alors que la teneur en quanta dans la lincomycine (42), la polymyxine B (37) et la clindamycine (32) se situe entre les valeurs trouvées dans le magnésium et dans la tubocurarine (123). La teneur témoin en quanta a été de 152. En présence d'un mélange de magnésium et de tubocurarine, il n'a pas été possible d'enregistrer le m.e.p.p. et la teneur en quanta a été de 39. Le blocage des crispations par un mélange de magnésium et de tubocurarine a été plus facilement inversé par un mélange de calcium et de néostigmine (à 70% des valeurs témoins) que par le calcium (à 49% des valeurs témoins) ou par la néostigmine (à 30% des valeurs témoins), seuls. Les blocages provoqués par la lincomycine et la polymyxine B ont été mal inversés par un mélange de deux agents d'inversion. On en a conclu que la streptomycine possède une action similaire à celle du magnésium alors que la lincomycine, la clindamycine et la polymyxine B ont des activités de blocage relatives moins pré-jonction et plus post-jonction. Cependant, les effets de la lincomycine et de la polymyxine B ne sont pas analogues à ceux d'un mélange de magnésium et de tubocurarine et leur mécanisme d'action n'est toujours pas clairement défini. La clindamycine a produit des effets compatibles avec l'activité anesthésiante locale.

UNTERDRÜCKUNG DER MITTLERSUBSTANZ UND DER POSTJUNKTIONALEN SENSITIVITÄT WÄHREND NEUROMUSKULÄRER BLOCKIERUNG DURCH ANTIBIOTIKA

ZUSAMMENFASSUNG

Um den Mechanismus zu studieren, durch den Antibiotika Muskellähmung herbeiführen, wurden die Wirkungen von Streptomycin, Lincomycin, Polymyxin B und Clindamycin in einem Mäuse-Diaphragma-Nerven-Zwerchfellhälfte-Präparat untersucht. Streptomycin ähnelte Magnesium durch die Reduzierung von Schwingung und Frequenz des Miniatur-Endplattenpotentials (m.e.p.p.), während Lincomycin, Clindamycin und Polymyxin B wie Tubocurarin m.e.p.p. eliminierten. Der Quantengehalt von Endplattenpotential (e.p.p.) betrug in Streptomycin 9, ähnlich wie in Magnesium (5), wogegen die Werte in Lincomycin (42), Polymyxin B (37) und Clindamycin (32)

zwischen den in Magnesium und in Tubcurarin (123) gefundenen Werten lagen. Der Kontrollwert betrug 152. In Anwesenheit einer Mischung von Magnesium und Tubocurarin konnte kein m.e.p.p. festgestellt werden, und der Quantengehalt betrug 39. Die Zuckungsblockierung durch eine solche Mischung konnte erfolgreicher durch eine Mischung von Kalzium und Neostigmin aufgehoben werden (zu 70% des Kontrollwertes) als durch Kalzium (zu 49% des Kontrollwertes) oder durch Neostigmin (zu 30% des Kontrollwertes) allein. Blockierungen durch Lincomycin und Polymycin B konnten nur schlecht durch eine Mischung dieser beiden Mittel aufgehoben werden. Daraus schliesst man, dass Streptomycin eine magnesiumartige Wirkung hat, während Lincomycin, Clindamycin und Polymyxin B eine relativ grossere postjunktionale und kleinere präjunktionale Wirkung haben. Allerdings waren die Wirkungen von Lincomycin und Polymixin B nicht analog zu denen einer Tubocurarin-Magnesiummischung, und ihr Mechanismus ist noch immer nicht klar. Clindamycin produzierte Wirkungen, die mit Lokalanästhesie vertraglich waren.

DEPRESION DE DESCARGA DEL TRANSMISOR Y SENSIBILIDAD POSTJUNCIONAL DURANTE BLOQUEO NEUROMUSCULAR CAUSADO POR ANTIBIOTICOS

SUMARIO

Con el objeto de descubrir los mecanismos mediante los cuales los antibióticos inducen parálisis muscular, se averiguaron los efectos de la estreptomicina, de la lincomicina, de la polimixina B y de la clindamicina en la preparación hemidiafragmo–nervio frénico del ratón. La estreptomicina se asemejaba al magnesio al reducir la amplitud y frecuencia del potencial de la placa terminal miniaturizada (p.p.t.m.), mientras que la lincomicina, la clindamicina y la polimixina B se parecían a la tubocurarina al eliminar el p.p.t.m. El contenido cuántico del potencial de la placa terminal (p.p.t.) en la estreptomicina era de 9, similar al que se encuentra en el magnesio (5), mientras que los contenidos cuánticos en la lincomicina (42), la polimixina B (37) y la clindamicina (32) se sitúan entre los valores encontrados en el magnesio y la tubocurarina (123). El contenido cuántico del control era de 152. En presencia de una mezcla de magnesio y de tubocurarina, no se pudo registrar ningún p.p.t.m. y el contenido cuántico era de 39. El bloqueo de las contracciones causado por una mezcla de magnesio y de tubocurarina pudo ser invertido con mayor éxito mediante una mezcla de calcio y de neoestigmina (hasta el 70% del control) que mediante el calcio solo (hasta el 49% del control) o la neoestigmina sola (hasta el 30% del control). La lincomicina y la polimixina B indujeron bloqueos cuya inversión por una mezcla de los dos agentes invertidores resultó bastante insatisfactoria. Se llega a la conclusión que la estreptomicina ejerce una acción parecida a la del magnesio, mientras que la lincomicina, la clindamicina y la polimixina B ejercen actividades bloqueadoras postjuncionales relativamente más fuertes, siendo las actividades prejuncionales mucho menos marcadas. Sin embargo, los efectos de la lincomicina y de la polimixina B no fueron análogos a los de una mezcla de magnesio y de tubocurarina y no se aclaró todavía su mecanismo de acción. La clindamicina tuvo efectos compatibles con la actividad anestética local.

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POLYMYXIN B AND HEART MUSCLE

Y. Z. SOHN AND R. L. KATZ

SUMMARY

The effects of the polypeptide antibiotic, polymyxin B, on myocardial contractility were studied in the isolated rat heart muscle. Five different doses of polymyxin B were tested. There were no changes in contractility with doses ranging from the clinical therapeutic value to three times greater. There was an initial increase and then depression with a dose six times greater than the therapeutic dose. There was no direct competitive interaction between polymyxin B and halothane or Ca^{2+}. This suggests that polymyxin B does not depress the myocardium in clinical doses and does not interfere with Ca^{2+} influx at the myocardial cell membrane.

It is well known that certain antibiotics can produce direct depression of the heart (Swain, Kiplinger and Brody, 1956; Cohen et al., 1970; Adams, 1976; Sohn and Katz, 1978) and induce neuromuscular paralysis (Pittinger and Adamson, 1972; Singh, Harvey and Marshall, 1978). There is some correlation between cardiac and neuromuscular activity. For example, penicillin neither depresses the heart nor induces neuromuscular paralysis. On the other hand, aminoglycoside antibiotics are direct cardiac depressants and produce neuromuscular block in clinical doses. Polymyxin B, a polypeptide, has been shown by experiment and clinical observation (Van Nyhuis, Miller and Fogdall, 1976) to have a strong neuromuscular blocking effect. Investigations in our department (Lee, Ricker and Katz, 1979) have shown that polymyxin B produced severe cardiovascular depression, but the mechanisms of action are not clear yet. We have evaluated the direct effect of polymyxin B on myocardial contractility.

METHOD

The isometric contractions of isolated rat heart muscle were examined. Isolated columns of left ventricular trabeculae carnae muscle were prepared. Each preparation was placed in an oxygenated (oxygen 95% and carbon dioxide 5%), 80-ml capacity muscle bath containing modified Krebs–bicarbonate solution, as described previously (Sohn and Katz, 1978). The temperature of the bath solution was held constant at 32 °C by a thermoregulator (Precision Scientific Co.). One end of the muscle was fixed and the other was connected to a Statham tension transducer (G 10 B–0.15–350) and its output recorded on one channel, while another output was connected to the differentiator (Optical Electronic Inc., Model 9009) and recorded on another channel of the recorder (Brush Recorder 440). This differentiator was checked at the factory using automatic test equipment and also at our laboratory.

Each muscle was stimulated with 2 × 8-mm platinum plate electrodes (placed about 10 mm apart, parallel to the muscle) at a frequency of 0.25 Hz with square wave pulse of 6.0 ms duration. In this preparation, no significant amount of catecholamine is released from the muscle (Koch-Weser, 1965). The length–tension curve of each preparation was determined after 30 min of isometric contractions. The average rat weight was 142.33 ± 10.97 g (mean ± SD) and maximum muscle length (the length at the peak of the length–tension curve) was 4.74 ± 0.64 mm.

Changes in muscle length, measured with a micrometer transformer, could be detected to 0.01 mm. The muscle length was held at the peak of the length–tension curve over the next 30 min for stabilization and then peak developed tension (T_{pd}), maximum rate of tension development ($+dP/dt$ max) and relaxation ($-dP/dt$ max) were recorded at a paper speed of 5 mm min^{-1}.

Polymyxin B studies

Polymyxin B (Pfizer) was prepared in a solution of 1 mg ml^{-1} in sterile water (Invenex). Doses of 0.64 mg (therapeutic dose in 80-ml bath) and 0.5, 2, 3 and 6 times this dose were chosen for dose–response studies. The final concentrations in the 80-ml bath were 5.708 µmol (A) and 0.5 (B), 2 (C), 3 (D) and 6 times (E) respectively. One selected dose was added directly to the muscle bath solution and changes in

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isometric contractions were recorded. After completion of the recording, the bath solution was drained, the muscle was washed twice with fresh modified Krebs–bicarbonate solution and the bath was refilled.

Interaction between polymyxin B and halothane

The muscles in the bath were exposed to 1.4% of halothane before (one group) and after (another group) concentration E of polymyxin B was added to the bath. T_{pd} and $\pm dP/dt$ max were recorded continuously at the same paper speed, 5 mm min^{-1}.

Gases were collected just below-bath. Halothane concentrations were determined with a Perkin-Elmer 900 gas chromatograph with a standard halothane concentration supplied by the company.

Interaction between polymyxin B and calcium

Concentrations D and E of polymyxin B were tested with 0.05, 0.1 and 0.2 ml of 10% calcium chloride (Elkins-Sinn, Inc.) which contain 0.034, 0.068 and 0.136 mmol litre^{-1} of Ca^{2+} respectively.

Two different recordings were made at the same paper speed of 5 mm min^{-1}. One was a continuous recording with Ca^{2+} added first and then polymyxin B. The other was with polymyxin B first and then Ca^{2+}.

Sterile water for injection USP

This was added in volumes (0.64 ml, ×0.5, ×2, ×3 and ×6) equal to those in the test groups, to evaluate the effect of the solvent itself.

RESULTS

Polymyxin B did not depress cardiac muscle contraction in clinical concentration or in higher concentrations up to three times greater (table I, fig. 1). A small initial increase in twitch was observed, but this was equal to that seen when the same volume of solvent was tested. In studies with the greatest concentration, E, of polymyxin B, initial increases and then slow progressive depressions were seen. About 30% depressions occurred at 30 min after administration of polymyxin B in concentration E (table I, figs 1 and 2). These depressions were progressive and

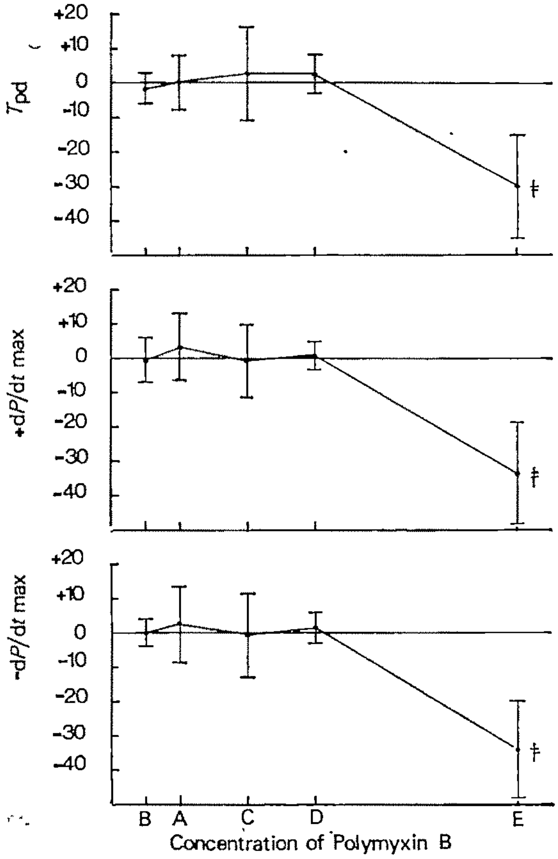

FIG. 1. Per cent changes of peak developed tension (T_{pd}), maximum rate of tension development ($+dP/dt$ max) and relaxation ($-dP/dt$ max) in response to polymyxin B. There were no changes with concentrations up to three times the therapeutic value, but significant depression with the greatest concentration. A = therapeutic concentration of polymyxin B (5.708 µmol); B = 5.708 µmol × 0.5; C = 5.708 µmol × 2; D = 5.708 µmol × 3; E = 5.708 µmol × 6; ‡$P < 0.05$.

TABLE I. *Direct effect of polymyxin B on isometric contractions of rat heart muscle. Polymyxin B 5.708 µmol is a final concentration in the 80-ml muscle bath and reflects the therapeutic concentration in blood (8 µg ml^{-1}). T_{pd} = peak developed tension; $+dP/dt$ max = maximum rate of tension development; $-dP/dt$ = maximum rate of tension relaxation.* ‡$P < 0.05$

	B	A	C	D	E
Polymyxin B 5.708 µmol	×0.5	×1	×2	×3	×6
Experiments performed	5	6	5	10	7
% Changes (mean ± SD)					
T_{pd}	−1.4±4.4	+0.2±7.9	+2.8±13.4	+2.4±5.2	−29.7±14.7‡
$+dP/dt$ max	−0.6±6.7	+3.4±9.7	−0.9±10.7	+0.9±4.1	−33.8±15.2‡
$-dP/dt$ max	0±3.7	+2.3±11.1	−0.7±12.3	+1.5±4.5	−34.2±15.4‡

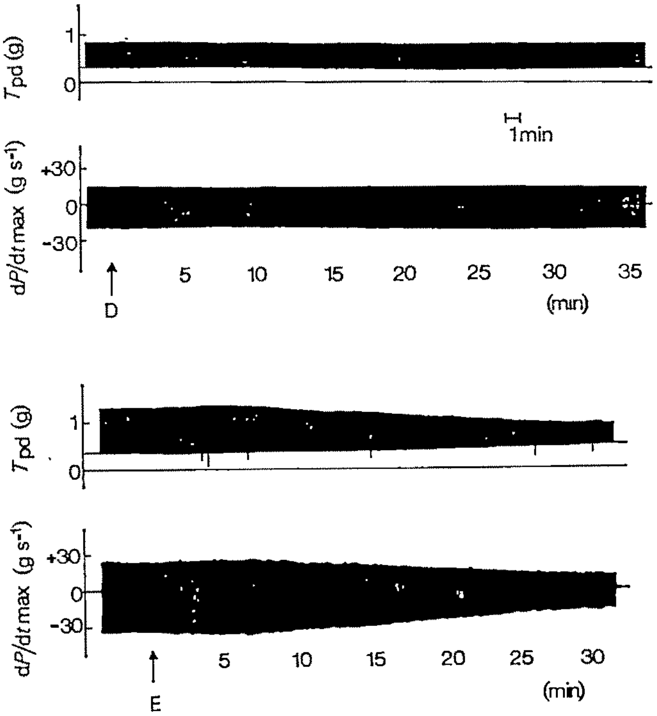

FIG. 2. Effects of high concentrations of polymyxin B on isometric contraction, showing no changes with 5.708 μmol × 3 (D) of polymyxin B, but progressive depression with 5.708 μmol × 6 (E) of polymyxin B. ↑ indicates the time of administration.

more than 80% depression occurred at 90 min after administration. These initial increases were produced by the same amount of solvent itself.

In the studies of concentration D of polymyxin B and 1.4% halothane, an interaction on isometric contraction was not seen. Polymyxin B in concentration D did not alter the direct effects of 1.4% halothane on myocardial contractility (fig. 3). In addition, 1.4% halothane depressed myocardium pretreated with polymyxin B to the same extent as halothane alone.

In the studies of interaction between polymyxin B and Ca^{2+}, concentration D or E of polymyxin B did not alter the magnitude of positive inotropic action of Ca^{2+} on heart muscle. Ca^{2+} caused the same degree of positive inotropy with concentration D

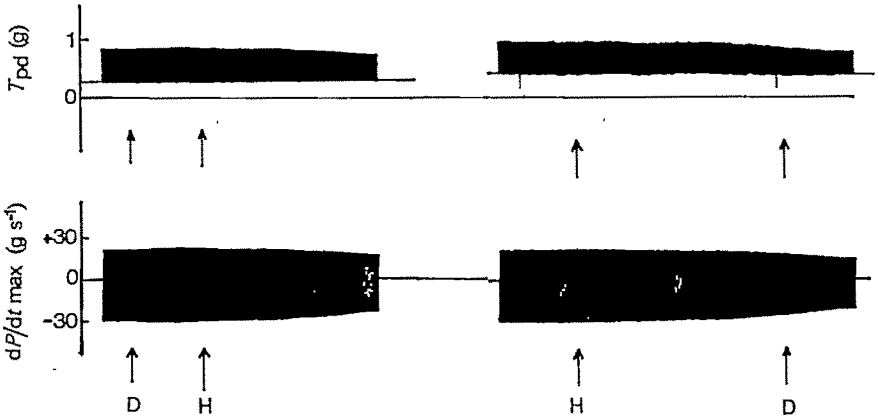

FIG. 3. Effect of polymyxin B and halothane on isometric contraction, showing no direct interaction. Polymyxin B did not alter the direct effect of halothane. D = 5.708 μmol × 3 of polymyxin B; H = 1.4% of halothane. ↑ indicates time of administration.

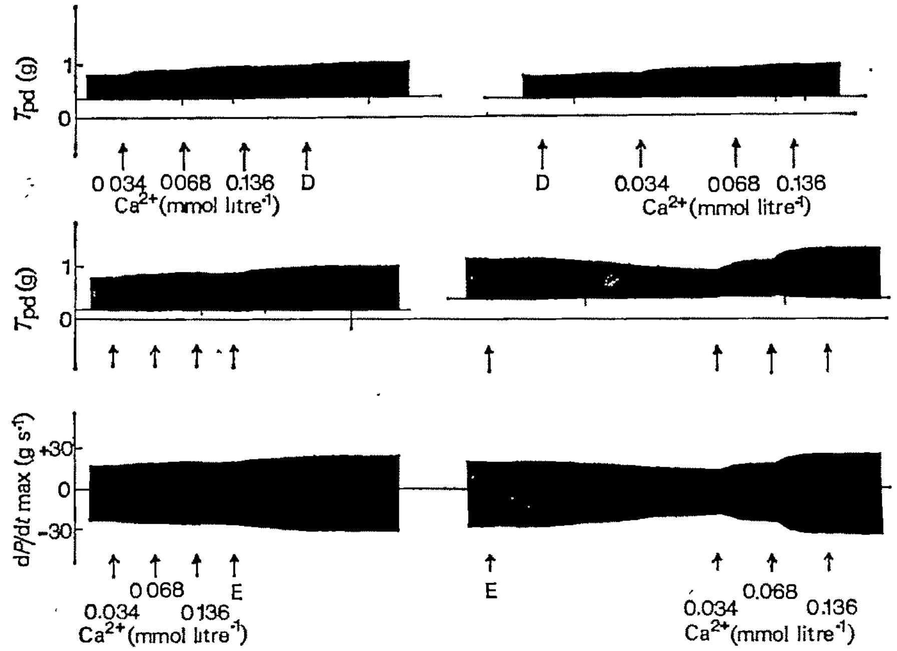

FIG. 4. Effect of polymyxin B and Ca^{2+} on isometric contraction, showing that 5.708 μmol × 3 (D) and 5.708 μmol × 6 (E) of polymyxin B did not alter the effect of Ca^{2+}, but a depression induced by concentration E could be restored to normal by Ca^{2+}. † indicates time of administration.

of polymyxin B-pretreated myocardium, but depression produced by concentration E of polymyxin B could be reversed to normal by Ca^{2+} (fig. 4).

DISCUSSION

Polymyxin B is among the very few membrane-active polypeptide antibiotics which show sufficient selective membrane toxicity and produce irreversible damage in cell membranes containing phosphatidylethanolamine as the dominant phospholipid (Hsu Chen and Feingold, 1973). Tissue phospholipid is located mainly in the cell membrane. One of its major functions is to contribute to the structure and function of cell membranes (Ansell, Hawthorne and Dawson, 1973). All biological membranes throughout nature are generally similar (Hsu Chen and Feingold, 1973) and all mammalian tissues contain, qualitatively, the same phospholipids but, quantitatively, different ones (Ansell, Hawthorne and Dawson, 1973). Thus one would expect polymyxin B to be clinically effective by affecting various host cell membranes.

Although the phosphatide content of the brain and the nervous system has been found to vary with age and development, nervous tissue possesses the largest phosphatide content of any of the organs and contains about three times as much as heart muscle (Wittcoff, 1951; Rouser, Nelson and Fleischer, 1968). Thus one would anticipate a neuromuscular blocking action of polymyxin B, particularly under anaesthesia involving a neuromuscular blocker, as reported in a recent article (Van Nyhuis, Miller and Fogdall, 1976). The early investigation of the phosphatide content of muscle showed that the heart contains the greatest percentage of phosphatides (Wittcoff, 1951). Since profound cardiovascular depression produced by polymyxin B was observed by other investigators (Lee, Ricker and Katz, 1979) and the mechanisms of action are not clear yet, we would postulate that polymyxin B may depress the cardiovascular system by means of (1) direct myocardial cell membrane damage similar to that seen in nervous tissue, (2) a direct ganglion blocking effect, (3) histamine release or (4) any combination of the above. So far, it has been reported that polymyxin B has a ganglion blocking effect and releases histamines (Naiman and Martin, 1967; Lee, Ricker, and Katz, 1979).

For studies of the direct effect of polymyxin B on heart muscle, the dose tested was chosen to reflect a blood concentration which can be achieved when polymyxin B is used to treat infection in man (up to

8 μg ml^{-1}). In an 80-ml muscle bath, the dose would be 640 μg (0.64 mg) which is equivalent to 5.708 μmol concentration. When polymyxin B is administered i.v., transient cardiac concentrations may be much greater than the clinical therapeutic concentration. Thus we performed these studies with clinical concentrations of polymyxin B in blood, 0.5, 2, 3 and 6 times greater than steady-state values. There were no depressant effects in clinical and greater concentrations (up to three times). Although initial increases in tension were seen, similar increases could be produced with the same amount of solvent alone. In studies with very large doses (6× clinical dose) progressive depression could be observed. Based on the work of Lee, Ricker and Katz (1979) and the present findings, we conclude that the causes of cardiovascular depression produced by clinical doses of polymyxin B are not a result of direct myocardial depression by polymyxin B but may be produced by direct sympathetic ganglion blocking effects of polymyxin B and histamine release.

Our results from heart muscle preparations are different from those of Van Nyhuis, Miller and Fogdall (1976), who showed a dose-dependent depression of the hemidiaphragm–phrenic nerve preparation. ED_{50} of polymyxin B (23 μg ml^{-1}) observed with skeletal muscle did not depress cardiac muscle contractility in our experiments.

In the studies by Van Nyhuis, Miller and Fogdall (1976) with therapeutic doses (5 μg ml^{-1}) of polymyxin B, the twitch tension was not depressed. These findings support the conclusion of Hsu Chen and Feingold (1973) that the polymyxin B susceptibility of biological membranes requires not only the presence of target sites in membrane such as phosphatidylethanolamine and a threshold density of these sites on the membrane surface, but also certain concentrations of polymyxin B. Myocardial depression produced by our large dose (6× clinical dose) of polymyxin B is likely to be a result of toxicity from massive overdose. Ca^{2+} exerted a positive inotropic effect in heart muscle with or without pretreatment with polymyxin B. Similar results were observed in the halothane and polymyxin B interaction studies.

In previous studies, the direct myocardial depression and neuromuscular blocking action produced by aminoglycoside antibiotics were antagonized readily by Ca^{2+} (Corrado, 1963; Sohn and Katz, 1978), but lack of antagonism of polymyxin B-induced paralysis by Ca^{2+} (Adamson, Marshall and Long, 1960; Naiman and Martin, 1967) probably indicates a different mechanism of action. Although a clinical dose of polymyxin B does not interfere with Ca^{2+} influx, depressions produced in cardiac muscle by large doses of polymyxin B can be restored to normal by Ca^{2+}. It appears that small fractions of phosphatidylethanolamine in myocardial cell membrane are damaged by polymyxin B, but other fractions of phospholipid in membrane continue to possess a high affinity for Ca^{2+} (Ansell, Hawthorne and Dawson, 1973).

In conclusion, clinical therapeutic doses of polymyxin B did not depress myocardial contractility, but massive overdoses did so. Clinical therapeutic doses do not produce any clinical side-effects but may produce undesirable effects in the presence of anaesthetic agents capable of producing depression.

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LA POLYMYXINE B ET LE MUSCLE DU COEUR

RESUME

On a procédé à une étude sur les effets qu'a l'antibiotique polypeptide: polymyxine B, sur la contractilité du myocarde, sur le muscle isolé du coeur d'un rat. On a essayé cinq doses différentes de polymyxine B. Il n'y a eu aucun changement dans la contractilité avec les doses allant de la plage des niveaux thérapeutiques cliniques aux doses trois fois supérieures. Il y a eu une augmentation initiale, suivie d'une dépression, avec une dose six fois plus forte que la dose thérapeutique. Il n'y a eu aucune interaction concurrente directe entre la polymyxine B et l'halothane. Ceci laisse penser que la polymyxine B ne déprime pas le myocarde lorsqu'on l'administre à des doses cliniques et ne gêne pas l'influx de Ca^{2+} à la membrane de la cellule myocardiale.

POLYMYXIN B UND DER HERZMUSKEL

ZUSAMMENFASSUNG

Die Wirkungen des Polypeptid-Antibiotikums Polymyxin B auf die myokardiale Kontraktionsfahigkeit wurde am isolierten Herzmuskel von Ratten studiert. Funf verschiedene Dosen wurden getestet. Es gab keine Veränderungen der Kontraktionsfähigkeit bei klinisch-therapeutischen Dosen bis zu Dosen, die 3 × grösser waren. Bei 6 × grosserer Dosis kam es zu einem anfänglichen Anstieg und dann einer Unterdrückung. Es gab keine direkte Wechselwirkung zwischen Polymyxin B und Halothan. Daher wird das Myokardium von Polymyxin B in klinischen Dosen nicht unterdruckt und wirkt sich auch nicht auf den Ca^{2+}-Eingang in der myokardialen Zellmembrane aus.

POLIMIXINA B Y EL MUSCULO CARDIACO

SUMARIO

Se estudiaron los efectos del antibiótico polipéptico, polimixina B, sobre la contractilidad miocardial en el músculo cárdiaco aislado de un ratón. Se hicieron pruebas con cinco dosis distintas de polimixina B. No hubo cambio en la contractilidad con dosis fluctuando del nivel terapéutico clínico hasta tres veces mayor. Hubo un aumento inicial seguido de una depresión con una dosis seis veces mayor de la dosis terapéutica. No hubo ninguna interacción competitiva directa entre la polimixina B y el halotano o el Ca^{2+}. Esto hace pensar que la polimixina B no deprime el miocardio en dosis clínicas y no interfiere con el influjo Ca^{2+} en la membrana celular miocardial.

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ASSESSMENT OF THE ANAESTHETIC AND METABOLIC ACTIVITIES OF DIOXYCHLORANE, A NEW HALOGENATED VOLATILE ANAESTHETIC AGENT

J. JARAMILLO AND J. R. CUMMINGS

SUMMARY

The ability of dioxychlorane to depress cortical activity in rats with implanted electrodes was compared to that reported previously for methoxyflurane, halothane and enflurane. Dioxychlorane was eight times more potent than enflurane, five times more potent than halothane and twice as potent as methoxyflurane. Serum fluoride concentrations after the administration of dioxychlorane and enflurane were not different from controls. In contrast, serum fluoride concentrations after methoxyflurane reached a value of 105 μmol litre^{-1} and remained increased for at least the next 48 h. Urine fluoride concentrations in the dioxychlorane and enflurane groups were a half and a quarter, respectively, of those recorded in the methoxyflurane group. Polyuria and polydipsia were observed only in the methoxyflurane group. Dilatation of the proximal convoluted tubules was noted in the rats anaesthetized with methoxyflurane. These changes were most marked at the 6- and 24-h periods following anaesthesia. Haemorrhage and ulcerative cystitis were noted in the bladders of the rats subjected to methoxyflurane. Cellular swelling in the proximal tubule was observed in the rats sacrificed 24 h after the administration of dioxychlorane. Enflurane produced no pathological changes.

Dioxychlorane (4,5 - dichloro - 2,2 - difluro - 1,3 - dioxolane; fig. 1) was synthetized in 1975 by Denson, Uyeno and Simon. Preliminary screening in mice suggested that dioxychlorane was an anaesthetic agent. Theoretically, it was expected to be an "inert" gas and, therefore, to exert its biological effects without undergoing chemical transformation during administration and residence in, and elimination from, the body (Denson and Simon, 1976; Denson et al., 1976; Uyeno et al., 1977).

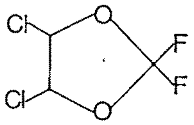

FIG. 1. Structural formula of dioxychlorane (4,5-dichloro-2,2-difluoro-1,3-dioxolane).

The present study was undertaken to assess the anaesthetic and metabolic activities of dioxychlorane. The anaesthetic activity was investigated by analysing the degree of cortical depression produced in Sprague–Dawley rats with implanted electrodes and comparing these effects with those reported previously (Jaramillo, 1978) for some clinically-employed fluorinated anaesthetics. The metabolic and renal studies were conducted in Fischer 344 rats, a strain which has been reported to be an unusually sensitive model for investigating fluoride-induced nephrotoxicity (Mazze, Cousins and Kosek, 1973). For comparative purposes an equal number of rats was anaesthetized with methoxyflurane or enflurane and, as in the case of dioxychlorane experiments, changes in body weight, food and water intake, urinary and serum fluoride concentrations, volume of urine excreted and histopathological effects on the kidney and bladder were examined.

MATERIALS AND METHODS

Permanent cortical electrodes were placed in 32 male Sprague–Dawley albino rats weighing 100–150 g at the beginning of the experiments. The methods described previously in detail (Jaramillo, 1978, 1979) for the implantation of electrodes and the recording and analysis of the electroencephalograms were followed.

For the metabolic studies, 3-month-old inbred male Fischer 344 rats weighing 180–220 g were used. The animals were placed in individual metabolic cages with food and water allowed *ad libitum* throughout the experiment. Seven days were allowed for the animals to adapt to their cages. Half of the rats were

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pretreated with phenobarbitone to cause enzyme induction (to enhance the metabolism of the anaesthetic agent). The animals were divided into eight treatment groups:

I:	Control—normal non-induced rats
II:	Control—phenobarbitone-induced rats
III:	Dioxychlorane 0.4%, non-induced rats
IV:	Dioxychlorane 0.2%, phenobarbitone-induced rats
V:	Methoxyflurane 0.5%, non-induced rats
VI:	Methoxyflurane 0.5%, phenobarbitone-induced rats
VII:	Enflurane 2%, non-induced rats
VIII:	Enflurane 2%, phenobarbitone-induced rats

Animals in groups II, IV, VI and VIII received 0.1% phenobarbitone *ad libitum* in the drinking water for 7 days. Methoxyflurane doses (0.5%, 3 h) were selected to produce moderate renal dysfunction (Mazze, Cousins and Kosek, 1972). Enflurane and dioxychlorane doses were selected to represent concentrations that are approximately equipotent with 0.5% methoxyflurane, according to the data obtained in this study (methoxyflurane 0.5%, dioxychlorane 0.2% and enflurane 2% for a period of 3 h). Control 24-h determinations of body weight, food and water intake and urinary flow were obtained. Daily urinary excretion of inorganic fluoride was monitored with an Orion ion-specific fluoride electrode and a Corning model 110 pH meter.

The anaesthetics were administered in a plastic chamber (50 cm long × 28 cm high × 28 cm wide). Methoxyflurane and dioxychlorane were vaporized in a Pentec 2 and enflurane in a Fluotec 3 vaporizer (both vaporizers were made by Cyprane Ltd, Keighley, Yorkshire). The Pentec 2 vaporizer was calibrated for use with dioxychlorane. The Fluotec 3 vaporizer, originally designed for use with halothane, has been reported (Dobkin et al., 1973) to supply concentrations of enflurane very close to its dial markings. Each anaesthetic was delivered for a period of 3 h. A constant flow (3 litre min^{-1}) of oxygen was delivered as a carrier gas at all times into the vaporizer, the outlet of which was connected to the anaesthetic chamber. The gases were delivered through an inlet port at one end of the anaesthetic chamber and suction was applied to the other end to take up the gases flowing through the chamber. An on-line water manometer monitored the resulting pressures to make certain the gases in the chamber remained at atmospheric pressure.

Anaesthetic concentrations in the chamber were monitored at 30-min intervals by means of a model 7610A Hewlett–Packard gas chromatograph. The gas chromatographic method employed helium as a carrier gas, a flame ionization detector and a 3.6 m × 2.8 cm-i.d. column packed with 15% QF1 maintained at 70 °C. Concentrations were calculated from peak height response compared with a standard curve which was prepared daily. After anaesthesia, the rats received oxygen alone until awake. They were then returned to their individual cages where 24-h body weight, food and water intake and urine collections were continued for the next 7 days.

Serum for inorganic fluoride determinations and kidney and bladder tissues for study by light microscopy were obtained from 52 additional rats treated as those in groups II ($n = 4$), IV ($n = 16$), VI ($n = 16$) and VIII ($n = 16$). Since no more than eight rats could be anaesthetized at a time, the anaesthetic procedure described above was repeated twice for each anaesthetic. Groups of four animals from each group were sacrificed immediately after anaesthesia and 6, 24 and 48 h later. At the time of sacrifice, the animals were anaesthetized with ether, and 5–6 ml of blood was removed rapidly in a syringe without anticoagulant by puncturing the abdominal aorta. Tissue samples from kidneys and bladders were removed and fixed in Bouin's solution; paraffin sections were prepared and stained with periodic acid–Schiff stain for study by light microscopy. All specimens were coded and examined without knowledge of the animal's treatment.

Statistical analysis

The electroencephalographic data were submitted to analysis of variance of parallel line assay (Finney, 1964). For the metabolic data the mean and SEM of each variable for each rat for the 4 days before anaesthesia were determined and means were calculated for each group. Daily means of postanaesthetic data were computed for each group and compared with the preanaesthetic means. Pre- to post-treatment differences were calculated for each group and intergroup comparisons were made. Paired t tests were used to test the significance of pre- to post-treatment differences within groups.

RESULTS

Effects on the electroencephalogram (e.e.g.)

Dioxychlorane produced changes in the e.e.g. characterized by the presence of spindle-like bursts and irregular, high-amplitude slow waves. As anaesthesia deepened, the amplitude of the spindle bursts and the slow-wave activity between bursts became progressively smaller until the burst suppression phase was reached. The intervals of iso-electric activity were prolonged progressively as the amplitude of spike bursts was reduced until the e.e.g. was totally flat in deepest anaesthesia (fig. 2).

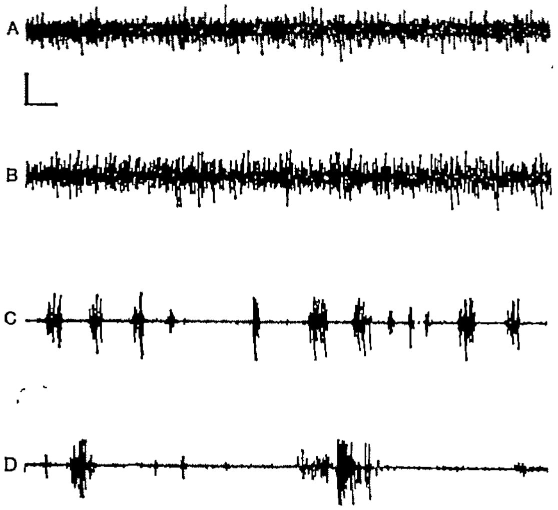

FIG. 2. Effects on the e.e.g. of increasing concentrations of dioxychlorane: A = control; B = 0.2%; C = 0.42%; D = 0.67%. The vertical calibration is 250 μV and the horizontal calibration is 4 s.

The histogram changes observed during anaesthesia were marked and consisted primarily of a shift of activity toward lower frequencies and a decrease in total activity. Figure 3 shows the baseline interval histogram and those taken 15 min after the administration of increasing concentrations of dioxychlorane. The modal period in the baseline histogram was 20 ms, which corresponds to a frequency of 50 Hz. The histograms taken after the administration of the anaesthetic show differences in several respects. First, there was a notable increase in low frequencies, which was interpreted to mean that the mean frequency of the histogram was less. For the 0.2% concentration, the modal frequency was approximately 40 Hz while those for the 0.42% and 0.67% concentrations were approximately 25 Hz and 20 Hz, respectively. Secondly, with increasing concentrations, there was an increased degree of cortical depression.

The degree of cortical depression was measured in our experiments by the amount of total brain activity. This value was obtained by noting the number of times the voltage crossed the zero line in the 3–5-min epoch during which the histogram was recorded. It is, therefore, a measure of the area under the curve of the histogram.

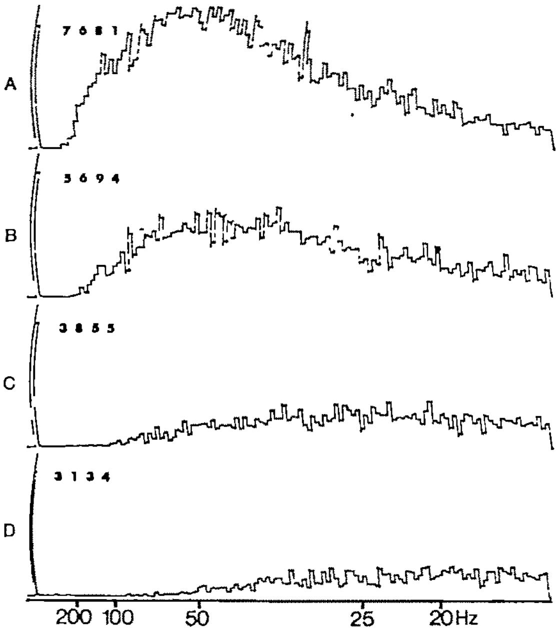

FIG. 3. Interval histograms taken before (A) and 15 min after administration of 0.2% (B), 0.42% (C) and 0.67% (D) concentrations of dioxychlorane. The numbers in the upper left corner represent the total brain activity present in each case.

Dioxychlorane produced, in a dose-dependent fashion, a decrease in total activity. Figure 4 shows the concentration–response line for dioxychlorane and compares it with those previously reported for methoxyflurane, halothane and enflurane, as obtained 15 min after commencement of anaesthesia. For methoxyflurane, halothane and enflurane the concentration values, as plotted in the x axis, are those dialed in the vaporizer. For dioxychlorane, the concentration values are:

Concentration set	Number of samples	Actual concentration
0.20%	7	0.18 ± 0.01%
0.35%	8	0.42 ± 0.02%
0.50%	9	0.67 ± 0.02%

TABLE I. *Comparative relative potencies (±95% confidence limits) of the compounds tested, as assessed over two (0–15 and 0–25 min) time periods. *Data obtained at the end of 15 min of anesthesia; †data obtained at the end of 25 min of anaesthesia*

	Enflurane	Halothane	Methoxyflurane	Dioxychlorane
Enflurane		1.53* (1.16–2.00)	3.90* (2.90–5.23)	7.67* (5.75–10.55)
Halothane	1.53† (1.06–2.13)		2.55* (1.94–3.37)	5.03* (3.83–6.83)
Methoxyflurane	4.03† (2.73–5.93)	2.64† (1.84–3.81)		1.97* (1.47–2.72)
Dioxychlorane	8.43† (5.80–13.05)	5.53† (3.88–8.45)	2.10† (1.44–3.26)	

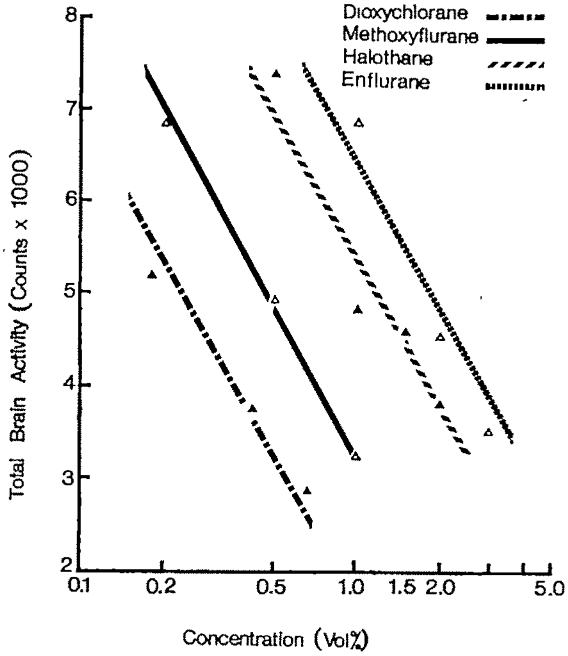

FIG. 4. Concentration–response line obtained for dioxychlorane, as compared with those previously reported for methoxyflurane, halothane and enflurane, 15 min after commencement of anaesthesia.

The parallel line analysis of variance covering all four volatile anaesthetics at the 15- and 25-min periods shows that:

(i) all four compounds evoke a highly significant dose–response relationship;
(ii) all four dose–response relationships are linear;
(iii) all four linear dose–response best-fitted lines are parallel;
(iv) all four lines are statistically different.

When listed in decreasing order of potency, dioxychlorane was the most active, followed by methoxyflurane, halothane and enflurane. Since statistical analysis of the data showed that the concentration–response lines are linear and parallel, relative potency values were calculated. Table I shows the relative potencies (±95% confidence limits) of the four compounds at the 15- and 25-min period after the administration of the drugs.

Table II depicts the recovery values for all of the compounds studied. Recovery values were obtained by measuring the area under the curve for the first 70 min after the withdrawal of the anaesthetic. This value is given as a percentage of the total area. The recovery values for dioxychlorane and methoxyflurane are not statistically different. If the compounds are listed in order according to their rate of recovery, dioxychlorane will be the slowest, followed by methoxyflurane, halothane and enflurane.

TABLE II. *Partial recovery from anaesthesia induced by four volatile anaesthetics. Area under the curve of the activity recorded 70 min after withdrawal of anaesthesia as compared with the value before anaesthesia. n.s. = not significantly different from dioxychlorane; **$P<0.01$; ***$P<0.001$, in comparison with dioxychlorane*

Compound	No. of rats	Per cent recovery (mean ± SEM)
Dioxychlorane	8	59.9 ± 3.2
Methoxyflurane	7	67.0 ± 1.9 n.s.
Halothane	8	72.9 ± 2.5**
Enflurane	9	77.8 ± 1.9***

Metabolic studies

Cumulative 4-day changes in body weights, food intake, water intake, urinary flow and fluoride excretion. Although plotting of the daily changes in body weight, food intake, water intake, urinary flow and fluoride excretion allows direct comparison of the time-course, onset, peak and duration of the effects of drugs, 4-day

TABLE III. *Metabolic effects observed after administration for 3 h of equipotent concentrations of the anaesthetics used. Figures shown are Δ values (cumulative values 4 days after anaesthesia minus cumulative values 4 days before anaesthesia) ± SEM and their statistical significance.* *$P<0.05$; **$P<0.01$; ***$P<0.001$ *compared with controls. n.s. = not significant. Numbers in parentheses indicate the vapour concentration administered to each group*

Experimental group	Enzyme induction	Body weight (g)	Food intake (g)	Water intake (ml)	Urinary volume (ml)	Urinary fluoride (μmol litre^{-1})
Control						
I	Non-induced	41.30	2.80	−1.50	0.72	0.68
		±6.36	±1.23	±2.31	±1.48	±0.47
II	Induced	29.17	−5.67	0.50	−3.13	−1.04
		±6.78	±6.40	±7.83	±6.46	±0.82
Dioxychlorane						
III	Non-induced	−40.00***	−27.00***	−32.11***	−10.10**	19.40***
	(0.4%)	±5.70	±3.36	±5.02	±2.58	±2.52
IV	Induced	−35.00***	−19.60 n.s.	−32.00**	−1.35 n.s.	20.20***
	(0.2%)	±10.99	±4.36	±7.15	±3.36	±2.18
Methoxyflurane						
V	Non-induced	11.63**	−1.38*	7.50*	6.75**	44.67***
	(0.5%)	±8.25	±1.02	±2.60	±1.45	±2.84
VI	Induced	−17.13**	−16.13 n.s.	27.75*	31.93**	56.31***
	(0.5%)	±11.80	±2.07	±5.50	±5.83	±3.34
Enflurane						
VII	Non-induced	14.56**	−7.00***	−13.44***	−4.87*	3.49***
	(2.0%)	±3.81	±2.07	±1.84	±1.51	±0.51
VIII	Induced	−4.44***	−8.78 n.s.	−2.00 n.s.	−3.38 n.s.	4.36***
	(2.0%)	±3.97	±1.59	±3.14	±1.50	±0.89

values are in most instances a more precise indication of the overall effect of a particular drug on these variables. Cumulative values in the present study were obtained by adding the values for the 4 "pre-drug" days and the 4 "post-drug" days. Table III shows the Δ values (and their statistical significance when compared with controls) obtained by subtracting the cumulative 4 "pre-drug" day values from the cumulative 4 "post-drug" day values. Control animals (whether treated with phenobarbitone or not) gained weight. All of the animals treated with phenobarbitone lost weight after anaesthesia. Non-induced animals gained weight with the exception of those treated with dioxychlorane (group III), which showed a considerable loss of weight. Variations in food intake among the control animals were not statistically significant. Food intake after anaesthesia was decreased in all treated groups but was statistically highly different ($P<0.001$) from control animals only for groups III and VII (dioxychlorane non-induced and enflurane non-induced, respectively). Animals treated with methoxyflurane (groups V and VI) showed an increase in water intake. All of the other animals showed a consistent decrease, especially the non-induced animals anaesthetized with enflurane and dioxychlorane (groups III and VII) in which the decrease in water intake was highly significant when compared with the controls. Similar quantitative results were obtained for the urine volumes. Methoxyflurane was the only anaesthetic to produce the polyuric disorder, particularly in the enzyme-induced animals.

Toxicity

All three anaesthetics tested increased significantly the amount of inorganic fluoride present in the urine. That present after methoxyflurane was considerably greater than the fluoruresis after dioxychlorane. Enflurane produced the least effect on the amount of urinary fluoride excreted. Enzyme induction did not appear to modify the amount of fluoride in the urine after enflurane, but it did have an effect after methoxyflurane. In the dioxychlorane group, the phenobarbitone-induced animals received only one-half the amount given to the non-induced, because the phenobarbitone-treated animals did not tolerate anaesthesia with dioxychlorane at a concentration of 0.4%.

While increases in the fluoride concentrations were found in the urine following the administration of all three anaesthetics, only the rats receiving methoxyflurane showed increased concentrations of inorganic fluoride in the blood. After 3 h of anaesthesia with 0.5% methoxyflurane, the serum fluoride concentrations increased from a control value of 17 μmol litre^{-1} to 105 μmol litre^{-1}. The concentrations of serum fluoride after dioxychlorane and enflurane were not significantly different from those found for the control animals. Serum fluoride concentrations after methoxyflurane remained increased for several days. Forty-eight hours after anaesthesia with methoxyflurane, the concentration of serum inorganic fluoride was still as great as 38 μmol litre^{-1}.

Light microscopy of the renal cortices of rats anaesthetized with methoxyflurane showed widespread dilatation of the proximal convoluted tubules. The height of the single layer of cuboidal cells composing the proximal tubule appeared to be reduced. However, nuclear alterations such as pyknosis or karyorrhexis were not present. A few foci of intraluminal sloughing of necrotic tubular epithelial cells were observed. The glomeruli were normal. The tubular changes were most marked at the 6- and 24-h periods after anaesthesia. Evidence of some tubular regeneration was seen in the 48-h group. Examination of the bladder of rats sacrificed 6 and 24 h after receiving methoxyflurane showed severe haemorrhagic and ulcerative cystitis. The bladders of the other rats receiving methoxyflurane were normal.

Rats receiving dioxychlorane and sacrificed 24 h later showed cellular swelling most notable in the proximal convoluted tubules. Some tubular changes were seen after dioxychlorane which resembled those described for methoxyflurane, but they were fewer in number and there was no evidence of necrosis. The bladders of these rats were normal. In comparison with the methoxyflurane experiments, dioxychlorane was markedly less nephrotoxic under the conditions of the study.

Rats anaesthetized with enflurane showed no pathological changes in the kidney or bladder as compared with the controls.

DISCUSSION

Dioxychlorane was found to produce changes in the e.e.g. that are characteristic of commonly-used inhalation anaesthetics. Dioxychlorane produced no unusual patterns of c.n.s. excitation. In contrast, such patterns are seen readily with enflurane at concentrations slightly greater than those used to induce anaesthesia. In respect of potency, dioxychlorane appears to be the most active known inhalation anaesthetic. Its potency ranges from 2 to 3 times that of methoxyflurane, the most potent of the currently-used inhalation anaesthetics. When compared with agents that have been considered recently for clinical use, dioxychlorane is considerably more potent than sevoflurane (Wallin et al., 1975) and aliflurane (Steen, Burgstedt and Holaday, 1976). The parallelism of the linear dose–response lines observed for all four compounds may indicate that these anaesthetic agents possess a similar mechanism of action in depressing brain activity. In this regard, it is interesting to note that the relative potency value for the 0–15-min period of anaesthesia is very similar to that for the 0–25-min period, for all of the compounds studied. A close relationship was found between potency and rate of recovery for the four anaesthetic agents tested. Therefore, the recovery from anaesthesia of animals under dioxychlorane was significantly slower than that for halothane and enflurane, but not statistically different from that observed for methoxyflurane.

Following exposure to anaesthetic concentrations of dioxychlorane, non-induced Fischer 344 rats showed significant decreases in body weight and food and water intake. Similar results were recorded in the methoxyflurane and enflurane experiments. The body weights after dioxychlorane were significantly less than those observed during the period before treatment for the same group of animals. The rate of growth for the animals receiving enflurane and methoxyflurane was decreased as compared with that of the controls, but these animals (in contrast to those receiving dioxychlorane) gained some weight in the period following anaesthesia. The food intake of all of the animals receiving anaesthesia was decreased in the period after anaesthesia as compared with the period before anaesthesia. This decrease was substantially greater for the dioxychlorane-treated animals. Contrary to the methoxyflurane group, all of the animals receiving either enflurane or dioxychlorane decreased their water consumption after anaesthesia.

In rats anaesthetized with methoxyflurane, statistically significant increases in urine volume and in serum and urinary inorganic fluoride concentrations occurred. However, following dioxychlorane and enflurane exposures in concentrations equipotent to that of methoxyflurane, urinary fluoride excretion during the first 4 days following anaesthesia was only 1/2 and 1/4, respectively, that of methoxyflurane. Moreover, neither polyuria nor polydipsia was observed in the animals exposed to dioxychlorane or enflurane. The threshold value for causing an untoward polyuria in Fischer 344 rats has been estimated to be 50 μmol litre^{-1} of serum inorganic fluoride (Cook et al., 1975). Once this value is exceeded the severity of the nephrotoxicity depends primarily upon the degree of increase and the duration for which increased concentrations of serum fluoride are maintained (Cousins et al., 1974). Subclinical renal toxicity has been reported to occur following methoxyflurane at serum inorganic fluoride concentrations of 50 μmol litre^{-1}, while clinical toxicity has been seen in patients in whom the serum inorganic fluoride exceeded 90 μmol litre^{-1} (Cousins and Mazze, 1973). Although the present study demonstrates that defluorination of the three anaesthetics took place in all of the animals (as indicated by increased urinary inorganic fluoride concentrations), the extent of increased defluorination following dioxychlorane and enflurane was considerably less than that seen with methoxyflurane. More important, peak serum fluoride concentrations after dioxychlorane and enflurane anaesthesia were not different from those obtained in control animals, whereas following methoxyflurane anaesthesia, serum fluoride concentrations peaked markedly and immediately after anaesthesia and then decreased very slowly. The prolonged increase of serum fluoride following administration of methoxyflurane or sodium fluoride has been associated with nephrotoxicity not only in animals (Frascino et al., 1972; Mazze, Cousins and Kosek, 1972, 1973; Bell, Hitt and Mazze, 1975; Brodeur et al., 1976), but also in humans (Taves et al., 1970; Mazze, Trudell and Cousins, 1971; Cousins and Mazze, 1973). As in man, the syndrome of renal dysfunction in our experiments was characterized, in the case of methoxyflurane, by polyuria. In contrast, dioxychlorane anaesthesia produced only a moderate, short-lasting increase in inorganic fluoride concentration in the urine and no increase in the urine volume or in the amount of fluoride in the serum. The nephrotoxic liability of dioxychlorane, although much less than methoxyflurane, is probably not absolute—especially when used in prolonged anaesthesia. Serum inorganic fluoride concentration, urinary volume and urinary fluoride excretion have been shown to increase with the total time that the animals are subjected to the anaesthetic (Uyeno et al., 1977). The degree of maximum polyuria and peak inorganic fluoride excretion has been reported by Barr and coworkers (1974) to be similar in animals receiving 2.5% enflurane for 10 h and those receiving 0.25% methoxyflurane for 1.5 h. However, serum fluoride concentrations in these investigators' enflurane group of animals at 24 h was only 16.0 μmol litre^{-1} in contrast to 65.7 μmol litre^{-1} in the group receiving methoxyflurane.

The present study shows that enzyme induction following phenobarbitone administration resulted in an increase in the metabolism of dioxychlorane. Enzyme induction in man as a result of exposure to various chemical substances such as barbiturates, tranquillizers, insecticides and aerosol sprays may exacerbate renal toxicity. Repeated administration of dioxychlorane may impose an increased risk of toxicity because of enzyme induction and residual concentrations of inorganic fluoride. Other factors may influence the toxicity of dioxychlorane adversely; for example, there appears to be a marked variation in the susceptibility of different individuals to fluoride as a nephrotoxin and a marked individual variation in metabolism of some anaesthetics for the same administered dose, resulting in markedly different serum inorganic fluoride concentrations (Cousins and Mazze, 1973).

Histopathological changes in the kidney in this study were considerably more pronounced in the group of animals anaesthetized with methoxyflurane than those given dioxychlorane or enflurane. A marked increase in urinary volume and pronounced histopathological changes indicated more renal damage in the methoxyflurane group than in the other groups. The occurrence of haemorrhagic cystitis in the methoxyflurane group has been reported previously by Mazze, Cousins and Kosek (1972). A similar frequency of this complication occurred after prolonged isoflurane (Cousins et al., 1973) and enflurane (Barr et al., 1974) anaesthesia in Fischer 344 rats. Haemorrhagic cystitis after these anaesthetics has not been reported in man and probably represents a species or organ-specific toxicity.

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EVALUATION DES ACTIVITES ANESTHESIQUES ET METABOLIQUES DU DIOXYCHLORANE, UN NOUVEL AGENT ANESTHESIANT HALOGENE ET VOLATIL

RESUME

La faculté que possède le dioxychlorane de déprimer l'activité corticale des rats auxquels on a implanté des électrodes, a été comparée à celle que l'on avait précédemment signalée pour le méthoxyflurane, l'halothane et l'enflurane. Le dioxychlorane est huit fois plus puissant que l'enflurane, cinq fois plus puissant que l'halothane et deux fois plus puissant que le méthoxyflurane. Les concentrations de fluorure dans le sérum, après l'administration de dioxychlorane et d'enflurane, n'ont pas été différentes des valeurs témoins. Par contre, après l'administration de méthoxyflurane, les concentrations de fluorure dans le sérum ont atteint une valeur de 105 μmol litre^{-1} et sont restées fortes pendant au moins les 48 heures suivantes. Les concentrations de fluorure dans l'urine, que l'on a trouvées dans les groupes traités au dioxychlorane et à l'enflurane, ont été de $\frac{1}{8}$ et $\frac{1}{4}$ respectivement de celles enregistrées pour le groupe traité au méthoxyflurane. On n'a observé de la polyurie et de la polydipsie que dans le groupe traité au méthoxyflurane. On a remarqué une dilatation des tubes contournés proximaux chez les rats anesthésiés au méthoxyflurane. Ces changements ont été particulièrement marqués entre 6 et 24 h après l'anesthésie. On a remarqué une hémorragie et une cystite ulcéreuse dans la vessie des rats traités au méthoxyflurane. Une enflure cellulaire du tube proximal a été observée chez les rats sacrifiés 24 h après l'administration de dioxychlorane. L'enflurane n'a causé aucun changement pathologique.

BEWERTUNG DER ANÄSTHETISCHEN UND STOFFWECHSEL-WIRKUNGEN VON DIOXYLCHLORAN, EINEM NEUEN, HALOGENIERTEN NARKOSEMITTEL

ZUSAMMENFASSUNG

Die Fähigkeit von Dioxylchloran zur Unterdrückung der kortikalen Aktivität in Ratten mit eingepflanzten Elektroden wurde mit der schon berichteten Wirkung von Methoxyfluran, Halothan und Enfluran verglichen. Dioxychloran war 8 × stärker als Enfluran, 5 × stärker als Halothan und

2× stärker als Methoxyfluran. Die Fluorid-Serumkonzentrationen nach Dioxychloran und Enfluran unterschieden sich nicht von den Kontrollwerten. Dagegen waren die Konzentrationen nach Methoxyfluran bei einem Wert von 105 µmol litre⁻¹, und blieben erhöht für mindestens die nächsten 48 Stunden. Urin-Fluoridkonzentrationen betrugen bei Dioxychloran und Enfluran jeweils 50% bezw. 25% der Konzentrationen bei Methoxyfluran. Polyuria und Polydipsia wurden nur in der Methoxyfluran Gruppe gefunden. Erweiterung der proximal gewundenen Tubuli wurde bei mit Methoxyfluran narkotisierten Ratten festgestellt. Diese Veränderungen waren am deutlichsten 6 und 24 Stunden nach der Narkose. Blutungen und ulzerative Zystitis wurden in den Blasen der mit Methoxyfluran behandelten Ratten festgestellt. Zellulare Schwellung in den proximalen Tubuli wurde in den 24 Stunden nach Dioxychloran-Verabreichung getoteten Ratten festgestellt. Enfluran bewirkte keine pathologischen Veränderungen.

EVALUACION DE LAS ACTIVIDADES ANESTETICAS Y METABOLICAS DEL DIOXICLORANO, UN NUEVO AGENTE ANESTETICO VOLATIL HALOGENADO

SUMARIO

Se procedió a la comparación de la capacidad del dioxiclorano para deprimir la actividad cortical en ratones a los cuales se insertaron electrodos, con la capacidad previamente indicada para el metoxiflurano, el halotano y el enflurano. El dioxiclorano tiene una potencia ocho veces mayor de la del enflurano, cinco veces mayor de la del halotano y dos veces mayor de la del metoxiflurano. Las concentraciones de fluoruro en el sero después de la administración de dioxiclorano y de enflurano no diferían de las de los controles. En cambio, las concentraciones de fluoruro en el sero después de la administración de metoxiflurano alcanzaron un valor de 105 µmol litre⁻¹ y permanecieron así durante las siguientes 48 h por lo menos. Las concentraciones de fluoruro en la orina en los grupos de dioxiclorano y de enflurano eran de ½ y de ¼ respectivamente en relación con las concentraciones registradas en el grupo del metoxiflurano. Se observaron poliuria y polidipsia en el grupo de metoxiflurano únicamente. Se notó una dilatación de los túbulos convolutados proximales en los ratones anestesiados con metoxiflurano. Estos cambios fueron particularmente marcados en los periodos de 6 y 24 h después de la anestesia. Se registró hemorragias y cistitis ulcerante en las vejías de los ratones sometidos a anestesia por metoxiflurano. Se observó inchazón celular en el túbulo proximal de los ratones beneficiados 24 h después de la administración de dioxiclorano. El enflurano no produjo ningún cambio patológico.

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AWARENESS DURING SURGERY—A NEW APPROACH

R. S. CORMACK

SUMMARY

With modern light anaesthesia the problem of awareness during surgery has defied analysis, because no physical sign reliably signals the conscious level. A test has been developed which entails direct communication with the patient at the end of surgery, noting the earliest moment after withdrawal of nitrous oxide at which he makes the appropriate response to a verbal request, the "time to correct response" (TCR). This test showed premedication with lorazepam 4 mg/70 kg to be significantly better than morphine 10 mg for ensuring unconsciousness when the main anaesthetic agent was nitrous oxide, in two groups of patients undergoing abdominal surgery ($P < 0.01$). All patients who had lorazepam were able, on request, to hold up the head a few minutes after surgery. Thus the benefits of light anaesthesia were retained whilst ensuring unconsciousness.

The virtues of opiates as a supplement to nitrous oxide are well known, but problems remain. Unpleasant recall of surgery occasionally happens with low dose regimes (Blacher, 1975; Wilson, Vaughan and Stephen, 1975), whilst greater doses sometimes lead to potentially lethal depression of breathing after surgery (Adams and Pybus, 1978). Both problems continue to be reported, verbally and in print, with all opiates including fentanyl. No infallible way of tailoring the dose to the individual has been devised and a *Lancet* editorial (1973) concluded: "Assessing the level of consciousness in a paralysed patient is a matter in which even the most experienced may occasionally be deceived." The beginner may be sorely tried.

It seemed worth testing lorazepam because, unlike morphine, it is an effective hypnotic in doses which do not depress breathing. The patient is drowsy but rousable. He is already part of the way towards sleep, so that adding nitrous oxide might render even the resistant patient unconscious. In a previous study (Cormack, Milledge and Hanning, 1977) we compared the respiratory effects of lorazepam and morphine, whilst the present study compares the same drugs in their effects on consciousness, using a new test presented recently to the Anaesthetic Research Society (Cormack, 1978).

PATIENTS AND METHODS

Two groups of fit adults were studied in 10 pairs roughly matched for age, sex and type of operation (usually hysterectomy).

Anaesthetic. Table I summarizes the two methods. The morphine group is labelled the "Bristol" method because the main feature is no hyperventilation, mean arterial $P\text{CO}_2$ 4.7 kPa (35 mm Hg). Following the elegant study by Clutton-Brock (1957) on the effects of hyperventilation it became common practice in Bristol to keep Pa_{CO_2} near normal. Otherwise it is a standard technique using nitrous oxide supplemented with morphine and myoneural blockade. The lorazepam group had the same anaesthetic, but with less thiopentone and less morphine supplement.

TABLE I. *Average doses and other details of the two groups*

	Bristol method	Lorazepam version
Mean age (yr)	38	40
Mean wt. (kg)	59	59
Premedication	Morphine 10 mg Atropine 0.6 mg	Lorazepam 3.4 mg Atropine 0.6 mg
Induction	Thiopentone 230 mg	Thiopentone 153 mg
Main agent	N_2O 70%	N_2O 70%
Supplement	Morphine 11 mg	Morphine 6 mg
Myoneural blocker	Pancuronium 4.9 mg	Pancuronium 4.7 mg
Pa_{CO_2} (kPa)	4.7	4.7

TCR test has been used in more than 500 patients and a detailed analysis is in preparation. In essence, after antagonizing the relaxant, nitrous oxide is turned off and the lungs ventilated with oxygen at the same minute volume as before. The patient is asked to open his mouth. If there is no response laryngoscopy and suction are carried out. This is repeated at 0.25-min intervals until the appropriate response is obtained.

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RESULTS

After morphine the mean TCR was 0.8 min, whereas after lorazepam it was 1.9 min (fig. 1), this difference being significant at the 1% level by either parametric (paired *t*) or non-parametric (Wilcoxon) tests. Consciousness returned more abruptly in the morphine group and typically the patient was unrousable one moment, but alert and co-operative 15 s later. After lorazepam the transition was more gradual and even after full co-operation was obtained some drowsiness remained.

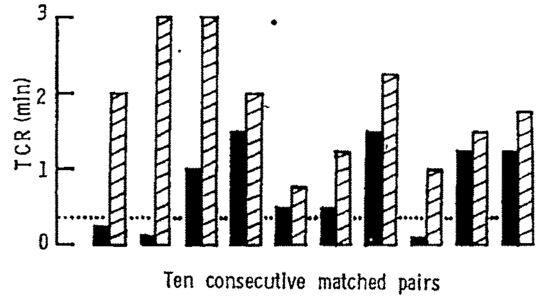

FIG. 1. Ten pairs of patients, matched for age, sex and type of operation, were studied at completion of surgery. The earliest moment after turning off nitrous oxide at which the patient made the appropriate response to a verbal request, the "time to correct response" (TCR), is shown. Values below the dotted line indicate awareness under anaesthesia. ■ = morphine; /// = lorazepam.

The brain nitrous oxide concentration cannot have changed appreciably in less than 15 s, allowing for mixing and circulation time, therefore responses in this period indicate awareness under anaesthesia. By this criterion three in the morphine group were awake, although none had any recall of this. Even the final laryngoscopy was not remembered, the first event recalled being the oxygen mask put on in the recovery ward. In the lorazepam group none was awake under nitrous oxide and amnesia persisted for some hours after operation.

The lorazepam findings have since been confirmed in more than 100 patients, the mean TCR being 1.8 min for operations lasting up to 3 h. However, in 10 patients having longer operations, of 3–8 h, the TCR was significantly shorter. Thus long operations may require a topping up dose of lorazepam, and this is being studied.

DISCUSSION

Choice of criterion. The unreliability of physical signs as a guide to the level of consciousness is becoming increasingly clear. Not only may florid signs occur in deeply unconscious patients, but the opposite is also true. It seems we are left with direct communication as the only meaningful test. If the patient makes the appropriate response to a verbal request, that is unlikely to be a reflex; it argues a degree of consciousness, however attenuated it may be.

There is nothing new about this approach. From John Snow onwards it has been used by many of the pioneers. The only new feature of the TCR test is timing the moment of waking. In effect this gives an index of the amount by which the nitrous oxide concentration must be reduced before consciousness can return. Thus it is quantitative, and the importance of this is explained below. Awareness without recall is also not a new finding and has often been reported with relaxant techniques. Its frequency can be estimated by the TCR test.

Design of the experiment. Much thought was given to the problem of making the trial double-blind. In the end this did not seem essential, because sedation and pain were not being measured, only an objective sign. If asked to open his mouth the patient either complies, or not, and there is little scope for observer bias. The experiment, as described, can be verified by any anaesthetist in his routine work.

The longer waking time after lorazepam cannot have been the result of differences in the dose of thiopentone, or morphine supplement, because both were deliberately reduced in the lorazepam group.

The morphine supplement was given as a single dose before surgery started, therefore its blood concentration would be least at the end, which applies also to the premedicant and thiopentone. It follows that if the patient was unrousable at the end, even with strong stimulation, the likelihood of his being awake before this is remote.

Awareness. The merits of the Bristol method are well established. Serious respiratory depression does not occur and naloxone is not used because the morphine dose is restricted to a value similar to that which has proved safe, over 50 years, in the wards. However, in the last 1000 cases anaesthetized by the author, unpleasant recall has occurred twice. Technical error was excluded and the patients appeared truthful. To react by increasing the dose of opiate would reduce safety after operation without necessarily solving the problem. Even a three-fold larger dose, with increments given in response to physical signs, did not always prevent unpleasant recall of surgery (Holmes, 1976).

However, a hypnotic premedication has greatly reduced the likelihood of awareness, despite a smaller dose of morphine. This conclusion was by no means obvious from the physical signs, such as reflex movement, but clear-cut from the TCR test. Moreover, the difference was apparent from quite a small sample, which illustrates the main purpose of the technique. By providing a quantitative, if approximate, estimate of the level of consciousness in each patient the TCR test greatly increases the sensitivity of comparisons between anaesthetics. Without such a test the statistical problems are daunting. Unpleasant recall is rare with all established methods, so with this yard-stick there is no alternative to large samples. For example, to improve on his previous results with the Bristol method (2 failures/1000) the author would have to show zero frequency in at least 5000 patients to be statistically convincing (by Fisher's exact test). Hence the slow pace of research in this field over the past two decades. In contrast, the TCR test makes it possible to conclude, from a small sample, that if unpleasant recall is uncommon with the Bristol method it must be rare almost to the point of exclusion with the lorazepam version.

To find the exact frequency, if any, of awareness with a new technique still requires a large sample. However, even if a large sample showed the occasional highly resistant patient to be awake under the combination of nitrous oxide and lorazepam, then unpleasant recall remains improbable because of the potent and prolonged amnesic action of this drug.

Amnesia. Some anaesthetists have hesitated to use lorazepam, precisely because of its amnesic effect. All our patients might be awake and, if recall of surgery were the sole guide, we would never find out. The TCR test allays these fears and shows the reality to be quite the opposite. It shows that a standard anaesthetic, which has given good results for decades, quite often creates an amnesic state rather than complete insensibility, but if the same technique is used after the standard premedication has been replaced with lorazepam the amnesic state may be converted to full unconsciousness.

Furthermore, with the lorazepam method the patient is awake before leaving the anaesthetist. It thus provides a compromise between the main opposing doctrines. On the one hand, the Bristol, Liverpool and related methods give very fast waking, but unpleasant recall occasionally happens. On the other hand, some have favoured a step back towards deeper anaesthesia by, for example, adding 0.5% halothane continuously to 70% nitrous oxide. This probably reduces the frequency of unpleasant recall—although this is far from certain (Moir, 1976)—but the patient is often unconscious for more than 20 min on leaving the anaesthetist. Lorazepam avoids both disadvantages.

The unique properties of nitrous oxide (Eger, 1974; Barth and Büchel, 1975) should make it the cornerstone of modern anaesthesia, but its popularity has suffered from its occasional failure adequately to anaesthetize the resistant patient and many, understandably, are given deeper anaesthesia than is in their best interests. Thus a supplement which made nitrous oxide, not just thoroughly safe, but also thoroughly reliable, would be welcome. For this role lorazepam is surely a strong contender, for this and other reasons (Cormack, 1979; Dundee et al., 1979).

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CONNAISSANCE PENDANT UNE INTERVENTION CHIRURGICALE: UN NOUVEAU POINT DE VUE

RESUME

Avec l'anesthésie légère moderne, le problème de la connaissance pendant une intervention chirurgicale a défié l'analyse, parce qu'aucun signe physique ne signale d'une manière fiable le niveau de l'état de conscience. On a mis au point un test, qui met en cause la communication directe avec le patient à la fin de l'intervention, en prenant note du premier moment auquel celui-ci fait une réponse appropriée à une question verbale, après le retrait du protoxyde d'azote; on a dénommé ce test TCR (time to correct response, soit: temps nécessaire pour obtenir une réponse correcte). Ce test a fait ressortir que la prémédication à l'aide de lorazépam (4 mg/70 kg) était nettement meilleure que la morphine (10 mg) pour s'assurer de la perte de conscience, lorsque le principal agent anesthésiant était le protoxyde d'azote et lorsqu'on l'a appliqué à deux groupes de malades subissant une intervention à l'abdomen ($P < 0{,}01$). Tous les malades auxquels on avait administré du lorazépam ont été en mesure de soulever leur tête quelques minutes après l'intervention et lorsqu'on le leur a demandé. On a donc conservé tous les avantages d'une anesthésie légère, tout en étant assuré d'un manque de connaissance.

WAHRNEHMUNGSFÄHIGKEIT BEI OPERATIONEN—EINE NEUE AUFFASSUNG

ZUSAMMENFASSUNG

Bei moderner Leichtnarkose war das Problem der Wahrnehmungsfahigkeit während der Operation nicht zu analysieren, weil sie durch keine verlässlichen physischen Signale angezeigt wurde. Nun wurde ein Test entwickelt, bei dem es zu direkter Kommunikation mit dem Patienten am Ende der Operation kommt, wobei der früheste Augenblick nach Entzug von Stickoxyd festgehalten wird, zu dem der Patient die entsprechende Reaktion auf eine gesprochene Anweisung zeigt—die "Zeit bis zur korrekten Reaktion" (TCR). Dieser Test ergab einen eindeutigen Vorteil von Vorbehandlung mit 4 mg/70 kg Lorazepam gegenuber 10 mg Morphium, was die Sicherung der fortdauernden Bewusstlosigkeit bei Stickoxyd als Hauptnarkosemittel betrifft; der Test wurde an zwei Gruppen von Patienten mit Unterleibseingriffen ($P < 0{,}001$) durchgeführt. Alle Patienten waren mit Lorazepam in der Lage, auf Aufforderung den Kopf einige Minuten lang hochzuhalte—schon wenige Minuten nach der Operation. So waren die Vorteile einer leichten Narkose beibehalten, und gleichzeitig Bewusstlosigkeit sichergestellt.

CONOCIMIENTO DURANTE INTERVENCIONES QUIRURGICAS—UN NUEVO ENFOQUE

SUMARIO

Con la anestesia ligera moderna, el problema del conocimiento durante las intervenciones quirúrgicas desafió el análisis, puesto que ninguna señal física indica de manera confiable el nivel del conocimiento. Se desarrolló una prueba que incluye la comunicación directa con el paciente al final de la intervención, observándose después de la remoción del óxido nitroso el primer momento en que responde de manera adecuada a una pregunta verbal, el "momento de respuesta correcta" (MRC). Esta prueba demostró que la premedicación con 4 mg/70 kg de lorazepam da mejores resultados que los obtenidos con 10 mg de morfina, para asegurar la pérdida de conocimiento, cuando se usa el óxido nitroso como agente anestético principal en dos grupos de pacientes sometidos a cirujía abdominal ($P < 0{,}01$). Todos los pacientes a quienes se administró lorazepam pudieron, cuando solicitados, levantar la cabeza unos minutos después de la operación. Entonces, se mantuvieron las ventajas de una anestesia ligera toda vez que se aseguraba la pérdida de conocimiento.

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PERCUTANEOUS CANNULATION OF THE DORSALIS PEDIS ARTERY

A prospective study

B. HUSUM, T. PALM AND J. ERIKSEN

SUMMARY

Strain-gauge plethysmography was used to determine the systolic arterial pressure in the great toe of 38 patients (aged 23–70 yr) undergoing lung surgery. In eight patients (21%) manual compression of the dorsalis pedis artery reduced the arterial pressure in the great toe to less than 40 mm Hg, and cannulation of the artery was not attempted. In 24 of 30 patients with adequate collateral arterial supply, a Teflon cannula (Venflon 1.20) was inserted percutaneously to the dorsalis pedis artery. Median cannulation time was 160 min. Six patients (25%, 95% confidence limits 10–47%) developed thrombosis of the artery and, in one, unsuccessful cannulation caused thrombosis. In two patients, recanalization of the artery occurred between the 2nd and the 8th day after operation. In four patients, examination 3–5 months after cannulation revealed a persisting decrease in the function of the dorsalis pedis artery. This suggests that the dorsalis pedis artery should not normally be selected for cannulation.

Cannulation of the dorsalis pedis artery (d.p.a.) is used for i.a. pressure monitoring or frequent sampling of arterial blood (Johnstone and Greenhow, 1973). Apart from a 6.7% frequency of thrombosis following cannulation of d.p.a. (Youngberg and Miller, 1976) there are few reported details of the risks of cannulating this vessel.

We have evaluated the frequency of thrombosis of d.p.a. following percutaneous cannulation and the systolic arterial pressure in the great toe in patients in whom d.p.a. was occluded following cannulation.

PATIENTS AND METHODS

Thirty-eight patients (12 female, 26 male) undergoing lung surgery were studied. The age range was 23–70 yr (median 57.5). None of the patients suffered from diabetes mellitus, arterial hypertension or symptoms of arteriosclerotic disease of the legs.

Before cannulation of d.p.a. the arterial pressure was determined simultaneously in the great toe of the foot chosen for cannulation and in the arm. Measurements of the pressure in the great toe were made following successive compression of d.p.a. and the posterior tibial artery. The pressure was determined using a two-channel strain-gauge plethysmograph. A 22-mm wide pneumatic cuff was placed around the proximal phalanx of the great toe and, as a volume detector, a mercury-in-rubber strain-gauge (Parks Electronics, Oregon) was placed around the distal phalanx of the great toe. This method was introduced by Strandness, Radke and Bell (1961) and Strandness and Bell (1965) and was described in detail in the monograph by Gundersen (1972).

If the collateral blood supply was adequate, as indicated by a systolic arterial pressure in the great toe in excess of 40 mm Hg (Lassen et al., 1975) when measured after compression of d.p.a., this artery was cannulated after induction of anaesthesia. A Teflon cannula (Venflon 1.20, Viggo, Sweden) was inserted percutaneously. Only one attempt at cannulation was allowed. The cannula was flushed regularly with heparinized saline.

Postoperative determinations of the arterial pressure in the great toe were performed on the 2nd and 8th day. If the arterial pressure in the great toe, measured with the posterior tibial artery compressed manually, had decreased by more than 25 mm Hg compared with the corresponding value before operation (2.5 times greater than the standard deviation of measurements performed under similar circumstances on different days (Gundersen, 1972; Nielsen, Bell and Lassen, 1972, 1973)) we regarded this as an indication of thrombosis of d.p.a. Throughout the examinations, corrections were made for changes in systemic arterial pressure. In the period after operation the skin of the back of the foot was examined for lesions or haematomata. The patients who developed thrombosis of d.p.a. were re-examined 3–5 months after operation.

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RESULTS

The d.p.a. pulse was palpable in all instances and all the patients had adequate blood supply to the great toe judged by the arterial pressure in the toe. In 25 of 38 patients compression of d.p.a. reduced the arterial pressure in the great toe (collateral supply was unable to compensate completely for the occlusion). In eight of 38 patients (21.1%, 95% confidence limits 9.6–37.3%) the arterial pressure in the great toe decreased to less than 40 mm Hg and consequently the collateral arterial supply was regarded as inadequate, and cannulation of d.p.a. was not attempted. These eight patients were in the same age range as the other patients (44–70 yr *v.* 23–70 yr).

In the 30 patients with adequate collateral supply cannulation of d.p.a. was performed successfully in 24 patients. The duration of cannulation ranged from 100 to 1800 min (median 160 min). None of the patients showed any evidence of tissue necrosis following cannulation.

Following cannulation of d.p.a., six patients (25%, 95% confidence limits 9.8–46.7%) developed thrombosis of the artery. This also occurred in one of the six patients in whom cannulation of d.p.a. was attempted unsuccessfully. The pressure determinations in the seven patients with thrombosis in the dorsalis pedis artery are shown in table I. Two of these (patients no. 23 and 24) had re-established perfusion through d.p.a. on the 8th day after operation. Four of the remaining five patients were re-examined 3–5 months after the operation; the vessel was still partly occluded (table II) but the collateral circulation was sufficient to ensure an adequate arterial pressure in the great toe.

DISCUSSION

The arterial supply to the foot consists of d.p.a., the posterior tibial artery and, to a lesser extent, the peroneal artery and the malleolar network. Earlier studies have indicated that in 3–14% of subjects d.p.a. cannot be palpated (Reich, 1934; Stephens, 1962; Barnhorst and Barner, 1968; Palm and Husum, 1978). Indeed, anatomical studies have shown d.p.a. to be absent in 3–12% of patients (Huber, 1941). In the present study d.p.a. was palpable in all patients.

Johnstone and Greenhow (1973) recommended cannulation of d.p.a. as a safe and reliable alternative

TABLE I. *Arterial pressure in the great toe, measured after manual compression of the posterior tibial artery, in six patients with thrombosis following cannulation of the dorsalis pedis artery and in one patient (no. 11) with thrombosis following unsuccessfully attempted cannulation of the dorsalis pedis artery*

Patient no.	Arterial pressure (mm Hg)				Duration of cannulation (min)
	Before cannulation	After cannulation			
		2nd day	8th day	3–5 months	
5	128	27	51	85	105
10	83	84	56	not examined	1800
14	77	52	22	48	120
20	78	24	25	40	260
23	60	20	90	not examined	120
24	70	20	99	not examined	210
11	120	56	52	62	not cannulated

TABLE II. *Arterial pressure in the arm and in the great toe determined simultaneously in three patients 3–5 months after development of thrombosis following cannulation of the dorsalis pedis artery. Corresponding pre-cannulation values are shown in brackets. In patient no.* 11 *the thrombosis developed after unsuccessfully attempted cannulation*

Patient no.	Arterial pressure (mm Hg)			Palpable dorsalis pedis artery pulse
	Arm	Great toe	Great toe after compression of posterior tibial artery	
5	142 (142)	97 (140)	85 (128)	yes
14	160 (122)	50 (76)	48 (77)	no
20	154 (138)	103 (86)	40 (78)	no
11	140 (150)	105 (108)	62 (120)	yes

to routine cannulation of the radial artery for monitoring purposes. They suggested that the existence of sufficient collateral flow could be evaluated by observing capillary refilling upon release of toe compression, but this test is difficult to use, especially when the feet are cold (Palm and Husum, 1978). Using a photoelectric pulse pick-up to detect collateral flow in the second toe following manual compression of d.p.a. Spoerel, Deimling and Aitken (1975) found that in 16% of patients d.p.a. appeared to carry almost the entire flow to the toes. In a recent study of the arterial dominance in the foot using strain-gauge plethysmography (Palm and Husum, 1978) no difference was found in the frequency with which d.p.a. or the posterior tibial artery dominated the arterial supply to the great toe.

Previous studies have not reported the number of patients in whom cannulation of d.p.a. was not performed because of inadequate collateral supply (Johnstone and Greenhow, 1973; Spoerel, Deimling and Aitken, 1975; Youngberg and Miller, 1976). A recent study of 100 young healthy subjects (Palm and Husum, 1978) demonstrated a 2% frequency of inadequate collateral supply as judged by a decrease in arterial pressure in the great toe to less than 40 mm Hg after manual compression of d.p.a. The 21% frequency of inadequate collateral supply found in the present study may be ascribed at least in part to the difference in age in the populations studied.

Our success rate of 80% (24 of 30) of attempted cannulations compares well with those reported by Johnstone and Greenhow (1973) (21 of 26) and by Youngberg and Miller (1976) (26 of 30).

The present study showed that despite a median cannulation time of only 160 min, the frequency of thrombosis of d.p.a. was as high as 25%. Using a Doppler flow technique Youngberg and Miller (1976) found thrombosis of d.p.a. in 6.7% of 30 patients after an average cannulation time of 492 min. Spoerel, Deimling and Aitken (1975) observed no complications in more than 100 patients following cannulation of d.p.a. for the duration of neurosurgical procedures. However, they did not quote the frequency of thrombosis of the artery or the cannulation time.

Signs of thrombosis of d.p.a. may develop some days after cannulation, but recanalization may occur (table I). In a study of cannulation of the radial artery Bedford and Wollmann (1973) found that thrombosis of the radial artery might develop as late as 7 days after removal of the cannula, and that recanalization of the vessel would occur most often within 70 days.

The results in table II indicate that, although the collaterals were sufficient to maintain arterial pressure in the great toe above critical values (40 mm Hg) 3–5 months after cannulation, the d.p.a. in none of these patients functioned as well as before cannulation. None of the patients had symptoms of inadequate blood supply to the feet.

Our present findings indicate that in 21% (10–39%) of our patients it would probably be unsafe to cannulate d.p.a. for monitoring purposes, as manual compression of the vessel would reduce the arterial pressure in the great toe to less than 40 mm Hg. If thrombosis should occur in the artery, the blood supply to the great toe could be permanently jeopardized. Of the patients with adequate collateral supply, 80% could probably be cannulated at the first attempt and 25% (10–47%) of these would develop thrombosis of d.p.a.

Because of these findings and because, in the older age group, arteriosclerosis may further adversely affect collateral circulation in the foot, we conclude that the dorsalis pedis artery should not be selected as a routine site for arterial cannulation.

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POSE SOUS-CUTANEE D'UNE CANULE DANS L'ARTERE PEDIEUSE

Une étude en perspective

RESUME

On a utilisé un pléthysmographe pour déterminer la pression artérielle systolique dans le gros orteil de 38 malades (âgés de 23 à 70 ans) subissant une intervention chirurgicale aux poumons. Sur 8 malades (21%), la compression manuelle de l'artère pédieuse a permis de réduire la pression artérielle dans le gros orteil à moins de 40 mm Hg et l'on n'a pas essayé de leur poser une canule dans l'artère. Sur 24 malades (parmi les 30 autres), ayant un débit artériel collatéral adéquat, on a inséré d'une manière sous-cutanée une canule en téflon (Venflon 1,20) dans l'artère pédieuse. Le temps moyen pendant lequel on a laissé la canule a été de 160 min. Six malades (25%, 95% des limites de confiance 10–47%) ont eu une thrombose de l'artère et, sur une personne, le fait de ne pas être arrivé à insérer la canule a provoqué une thrombose. Sur deux malades, la recanalisation de l'artère a été faite entre le deuxième et le huitième jour suivant l'intervention. Sur quatre malades, un examen effectué de 3–5 mois après la pose de la canule a révélé une diminution persistante de la fonction de l'artère pédieuse. Ceci permet de dire que l'artère pédieuse ne doit normalement pas être choisie pour la pose d'une canule.

PERKUTANE KANÜLENEINFÜHRUNG IN DIE DORSALIS PEDIS-ARTERIE

Eine vorbereitende Studie

ZUSAMMENFASSUNG

Filterlehre-Plethysmographie wurde verwendet, um den systolischen arteriellen Druck in der grossen Zehe von 38 Patienten (23–70 Jahre alt) bei Lungenoperationen zu bestimmen. Bei acht Patienten (21%) wurde durch manuellen Druck auf die dorsalis pedis-Arterie der arterielle Druck in der grossen Zehe auf unter 40 mm Hg reduziert, und Kanüleneinfuhrung in die Arterie wurde nicht versucht. Bei 24 von 30 Patienten mit ausreichender arterieller Blutzufuhr wurde eine Teflonkanüle (Venflon 1,20) perkutan eingeführt, mit einer mittleren Einfuhrungszeit von 160 min. Sechs Patienten (25%, 95% Vertrauensgrenzen 10–47%) entwickelten eine Thrombose der dorsalis pedis-Arterie, und bei einem Patienten bewirkte eine erfolglose Kanüleneinführung eine Thrombose. Bei zwei Patienten erfolgte die Rekanalisation der Arterie zwischen zweiten und achten Tag nach dem Eingriff. Bei vier Patienten stellte man 3–5 Monate nach Kanüleneinführung eine beständige Funktionssenkung der Arterie fest, was andeutet, dass die dorsalis pedis-Arterie normalerweise nicht fur Kanüleneinfuhrung gewählt werden sollte.

CANULACION PERCUTANEA DE LA ARTERIA PEDIA

SUMARIO

Se usó la pletismografía de medidor de presión para determinar la presión arterial sistólica en el dedo grueso del pie de 38 pacientes (de 23 a 70 años de edad) sometidos a cirujía pulmonar. En ocho pacientes (21%), la compresion manual de la arteria pedia redujo la presion arterial en el dedo grueso del pie hasta menos de 40 mm Hg, y no se intentó la canulación de la arteria. En 24 de los 30 pacientes con flujo arterial colateral adecuado, se introdujo percutáneamente una cánula de Teflón (Venflón 1,20) en la arteria pedia. El tiempo medio de canulación fue de 160 min. En seis pacientes (un 25%, con límites confiables del 95%, 10–47%) se registraron señales de trombosis de la arteria y en uno, falló la canulación, lo que causó trombosis al paciente. En dos pacientes, la recanalización de la arteria ocurrió entre el segundo y el octavo día después de la operación. En cuatro pacientes, el examen efectuado de 3 a 5 meses después de la canulación reveló una disminución persistente de la función de la arteria pedia. Esto indica que normalmente no se debe escoger la arteria pedia para efectuar canulaciones.

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MATERNAL BLOOD-GAS TENSIONS ($P\mathrm{A}_{\mathrm{O}_2}-P\mathrm{a}_{\mathrm{O}_2}$), PHYSIOLOGICAL SHUNT AND $V\mathrm{D}/V\mathrm{T}$ DURING GENERAL ANAESTHESIA FOR CAESAREAN SECTION

G. Lyons and M. E. Tunstall

SUMMARY

Measurements of maternal blood-gas tensions, ($P\mathrm{A}_{\mathrm{O}_2}-P\mathrm{a}_{\mathrm{O}_2}$), calculated pulmonary venous admixture (physiological shunt) and deadspace/tidal volume ratio ($V\mathrm{D}/V\mathrm{T}$) were made in 14 patients undergoing Caesarean section. Measurements were carried out after the induction of general anaesthesia, and before delivery, with the patient tilted to the left. With a mean inspired oxygen concentration of 67.5% mean $P\mathrm{a}_{\mathrm{O}_2}$ was 44.3 kPa, mean ($P\mathrm{A}_{\mathrm{O}_2}-P\mathrm{a}_{\mathrm{O}_2}$) 18.4 kPa, mean $V\mathrm{D}/V\mathrm{T}$ 32% and mean physiological shunt 9.5%. The findings are compared with published values for non-anaesthetized pregnant patients.

Studies of maternal oxygenation at delivery during general anaesthesia for Caesarean section have shown that the mean $P\mathrm{a}_{\mathrm{O}_2}$ for a given $F\mathrm{I}_{\mathrm{O}_2}$ have been less than values predicted from spontaneously breathing patients. In addition, they have shown great variation between individuals and between different studies (table I).

TABLE I. *Published maternal inspired oxygen concentrations, and arterial oxygen and carbon dioxide tensions, with standard errors in parentheses, at delivery by Caesarean section during general anaesthesia*

	$F\mathrm{I}_{\mathrm{O}_2}$ (%)	$P\mathrm{a}_{\mathrm{O}_2}$ (kPa)	$P\mathrm{a}_{\mathrm{CO}_2}$ (kPa)
Rorke, Davy and Du Toit (1968)	65	34.0 (1.8)	3.7 (0.1)
Houle, Fox and Gertel (1969)	50	27.2 (1.1)	4.9 (0.1)
Fox and Houle (1971)	29	13.9 (1.6)	4.3 (0.1)
Marx and Mateo (1971)	65	37.7 (1.3)	4.0 (0.1)
Magno and others (1976)	50	27.8 (2.7)	4.8 (0.2)
Palahniuk and others (1977)	99	41.1 (5.3)	4.3 (0.2)

Similar measurements in the Aberdeen Maternity Hospital have revealed a wide range of results for a given $F\mathrm{I}_{\mathrm{O}_2}$ value which could not be attributed to sampling technique or to method. In general surgical patients Campbell, Nunn and Peckett (1958) demonstrated a significant increase in physiological deadspace ($V\mathrm{D}$), and considerable individual variation in the change of alveolar–arterial oxygen tension differences ($P\mathrm{A}_{\mathrm{O}_2}-P\mathrm{a}_{\mathrm{O}_2}$), when artificial ventilation during anaesthesia was substituted for spontaneous ventilation when awake. Similarly, Hedenstierna and McCarthy (1975) showed that ($P\mathrm{A}_{\mathrm{O}_2}-P\mathrm{a}_{\mathrm{O}_2}$) was significantly greater with artificial ventilation, and that $V\mathrm{D}$ increased with increasing tidal volume ($V\mathrm{T}$).

This study was undertaken to measure these indices in patients undergoing artificial ventilation during Caesarean section, in the interval before delivery. The opportunity for comparing the results found in non-anaesthetized pregnant patients was provided by the studies of Templeton and Kelman (1976) made in the same unit.

PATIENTS AND METHODS

Patients

Fourteen unselected patients undergoing elective Caesarean section were studied. Two had severe pre-eclampsia according to the criteria of Nelson (1955). The indications for operation were various.

Anaesthetic technique

All patients had received 15 ml of magnesium trisilicate mixture, B.P.C. and were placed in a left lateral tilt sufficient to cause an obvious visual displacement of the uterus to the left. The induction sequence was pre-oxygenation, i.v. atropine 0.6 mg or hyoscine 0.4 mg, thiopentone 250 mg, suxamethonium 100 mg, cricoid pressure, and intubation of the trachea with an 8-mm cuffed tube. Maintenance of anaesthesia to delivery was with oxygen

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8 litre min^{-1}, nitrous oxide 4 litre min^{-1} and halothane from a specially calibrated vaporizer set to 0.4%. Non-rebreathing artificial ventilation was maintained with a Blease Manley ventilator at a tidal volume of approximately 700 ml and at a pressure not exceeding 2.9 kPa. Neuromuscular blockade was maintained with a suxamethonium infusion 0.4%, tubocurarine or pancuronium.

Measurement technique

Samples of blood were taken from the left radial artery for estimation of haemoglobin concentration, Pa_{O_2}, Pa_{CO_2} and pH. Expired gas was diverted into a canvas Douglas bag using an Ambu E valve in the patient breathing system. Both the inspiratory and expiratory tubing of the ventilator were attached to the input of the valve so that gas compressed in the ventilator tubing was vented through the expiratory port of the ventilator. The expired gas collection was used for the estimation of mixed expired oxygen and carbon dioxide percentages ($F\mathrm{E}_{O_2}$ and $F\mathrm{E}_{CO_2}$). Tidal volume was calculated by dividing the collected volume by the number of inflations; the latter was recorded using a pressure transducer between the inspiratory and expiratory tubing of the ventilator, and a Devices single channel recorder. Bag volumes were measured during emptying using a previously calibrated Wright's respirometer. Since the Wright's respirometer is designed for use with cyclical flows, a bench experiment was set up later to compare the performance of the Wright's respirometer with a previously calibrated dry gas meter in the emptying of a Douglas bag, and a correction factor was calculated.

Pa_{O_2}, Pa_{CO_2} and pH were measured with the Radiometer ABL 1 apparatus. Measured blood-gas tensions were corrected for the temperature differences between the subject and the measuring electrode, and for delay between sampling and measurement, using the nomograms of Kelman and Nunn (1966).

$F\mathrm{I}_{O_2}$ and $F\mathrm{E}_{O_2}$ were measured with a Servomex Paramagnetic Oxygen Analyser. $F\mathrm{E}_{CO_2}$ was measured with a Radiometer electrode type E5036 in nine patients and a Beckman LB2 medical gas analyser in five patients; conversions from tension to percentage and *vice versa* were calculated from the barometric pressure.

Equations for the calculation of $P\mathrm{A}_{O_2}$ and $V\mathrm{D}/V\mathrm{T}$ were those given by Fisher and Prys-Roberts (1968). Venous admixture was calculated using a modified form of the shunt equation applicable when $P\mathrm{A}_{O_2}$ was great enough to saturate haemoglobin fully in pulmonary capillary blood (greater than 26 kPa) (Laver and Seifen, 1965). The arterio–venous oxygen content difference was assumed to be 4 ml.

Samples were collected after 5 min of anaesthesia and before the uterus was opened. The mean induction–delivery interval was 19.4 min. Apparatus deadspace was 25 ml. Mean $F\mathrm{I}_{O_2}$ was 0.675 (SEM 0.7).

RESULTS

The results are shown in table II and may be compared with Templeton and Kelman's (1976) findings in non-anaesthetized pregnant patients (table IIb). Compared with (b), in (a) there are increases in $V\mathrm{D}$, $V\mathrm{D}/V\mathrm{T}$, ($P\mathrm{A}_{O_2}-Pa_{O_2}$) and physio-

TABLE II. *Pulmonary ventilation, arterial blood-gas tensions, ($P\mathrm{A}_{O_2}-Pa_{O_2}$), physiological shunt and $V\mathrm{D}/V\mathrm{T}$ ratio (a) during general anaesthesia before delivery by Caesarean section in* 14 *patients, and (b) in* 20 *normal pregnant patients at* 38 *weeks gestation, from figures published by Templeton and Kelman* (1976)

	(a)		(b)
	Mean ± SEM	Range	Mean ± SEM
Weight (kg)	65.0 ± 3.1	49.6–94.6	72.70 ± 1.5
Hb (g dl^{-1})	10.96 ± 0.35	8.3–12.7	11.00 ± 0.2
$V\mathrm{T}$ (litre, BTPS)	0.62 ± 0.02	0.49–0.77	0.65 ± 0.04
$V\mathrm{D}$ (litre, BTPS)	0.20 ± 0.02	0.13–0.36	0.18 ± 0.01
$V\mathrm{D}/V\mathrm{T}$	0.32 ± 0.03	0.19–0.53	0.30 ± 0.02
Pa_{O_2} (kPa)	44.3 ± 1.8	31.4–51.3	13.60 ± 0.1
Pa_{CO_2} (kPa)	3.1 ± 0.1	2.4–3.8	4.10 ± 0.1
pH (units)	7.503 ± 0.013	7.409–7.563	7.43 ± 0.006
Base deficit (mmol litre^{-1})	3.87 ± 0.46	1.1–6.2	3.10 ± 0.2
($P\mathrm{A}_{O_2}-Pa_{O_2}$) (kPa)	18.4 ± 2.3	7.6–29.7	2.15 ± 0.1
Physiological shunt (%)	9.46 ± 1.08	2.4–16.9	3.30 ± 0.2

logical shunt values. Mean Pa_{O_2} values are greater than in the two series quoted in table I with the same FI_{O_2}. In the two patients with severe pre-eclampsia ($PA_{O_2}-Pa_{O_2}$) and physiological shunt were 11.2 kPa and 5.1%, and 28.2 kPa and 14.1% respectively.

DISCUSSION

In surgical patients Nunn, Bergman and Coleman (1965) found ($PA_{O_2}-Pa_{O_2}$) ranged from 5 to 31 kPa where mean PA_{O_2} was 88 kPa. Marshall and Wyche (1972) demonstrated increases in ($PA_{O_2}-Pa_{O_2}$) and in venous admixture during anaesthesia in surgical patients. The degree of venous admixture ranged from 2.4% to 16.9%, with a mean value of 9.5%: Previously reported values during general anaesthesia with controlled ventilation in surgical patients range from 9% to 17% (Marshall and Wyche, 1972). Many of these studies used assumed values for the arterio–venous oxygen content difference ($Ca_{O_2}-C\bar{v}_{O_2}$). In this study ($Ca_{O_2}-C\bar{v}_{O_2}$) was assumed to be 4 ml dl^{-1}, although this assumption is arbitrary. Palmer and Walker (1949) found a value of 4.4 ml dl^{-1} in late pregnancy, but this was from a right atrial sample, in supine patients. Similarly, Hamilton (1949) found values of 4.84 ml dl^{-1} during the third trimester, and 5.52 ml dl^{-1} for the last 3 weeks of pregnancy. Where in previous studies an assumed value for ($Ca_{O_2}-C\bar{v}_{O_2}$) has been used to calculate venous admixture, it has been assumed to be the same value in the anaesthetized patient as in the awake. However, when measured during anaesthesia it was usually reduced (Marshall and Wyche, 1972). In this study the patient's lungs were hyperventilated by comparison with the practice in general surgical patients, but the values of Pa_{CO_2} recorded are in keeping with those found in women in labour (Crawford, 1972). This, in addition to the varying effects of the different premedicant and relaxant drugs on heart rate and cardiac output, will affect ($Ca_{O_2}-C\bar{v}_{O_2}$) and therefore Qs/QT. If the assumed values for ($Ca_{O_2}-C\bar{v}_{O_2}$) were taken to be either 5 ml dl^{-1} or 3 ml dl^{-1}, then calculated mean venous admixture would be in the region of 7% and 12% respectively.

Templeton and Kelman (1977) found a significant increase in ($PA_{O_2}-Pa_{O_2}$) and percentage shunt in patients with severe pre-eclampsia compared with normal pregnant patients. The two patients in our series with severe pre-eclampsia were not at the extremes of the range of values. One cannot predict in which direction their results would have been altered had they not been suffering from severe pre-eclampsia.

VD/VT ranged from 0.19 to 0.53 with a mean value of 0.32. This figure becomes 0.35 if the correction factor for the volume measurement is applied. These values are corrected for apparatus deadspace. Nunn, Bergman and Coleman (1965) found a similar range in anaesthetized surgical patients, and ratios of 0.30 are considered normal for healthy, intubated anaesthetized patients (Nunn, 1977).

Mean values for VD/VT, ($PA_{O_2}-Pa_{O_2}$) and calculated venous admixture all fall within the accepted range for anaesthetized surgical patients. This would indicate that factors peculiar to pregnancy, such as elevation of the diaphragm, and caval compression, have not played a significant part. However, the range of results indicates that this might not be true for the individual patient.

Strict comparisons of Pa_{O_2} cannot be made with other series because of differences in anaesthetic technique. Pa_{CO_2} was less in this series than in that of Rorke, Davy and Du Toit (1968) and Marx and Mateo (1971) (table I). Also, the induction–delivery interval in the former series was more than 45 min and the patients were not in lateral tilt. The range of Pa_{O_2} results is similar to that which can be expected in any investigation where maternal arterial blood is sampled at delivery during general anaesthesia for Caesarean section. In general it is not possible to predict those mothers who will have a much smaller than expected arterial oxygen tension in relation to inspired oxygen tension. Therefore, to be certain of providing adequate oxygenation for the fetus at Caesarean section, a relatively great maternal inspired oxygen concentration should be used.

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TENSIONS GAZ-SANG MATERNEL, $(PA_{O_2}-Pa_{O_2})$ SHUNT PHYSIOLOGIQUE ET V_D/V_T PENDANT UNE ANESTHESIE GENERALE POUR UNE OPERATION CESARIENNE

RESUME

On a mesuré les tensions gaz-sang maternel, $(PA_{O_2}-Pa_{O_2})$, mélange veineux pulmonaire (shunt physiologique) calculé ainsi que le rapport espace-mort/volume courant, sur 14 patientes subissant une opération césarienne. Les mesures ont été prises après l'induction de l'anesthésie générale et avant l'accouchement, la patiente étant inclinée vers la gauche. Lorsque la concentration moyenne d'oxygène inspiré a été de 67,5%, la Pa_{O_2} moyenne a été de 44,3 kPa, la moyenne $(PA_{O_2}-Pa_{O_2})$ de 18,4 kPa, le V_D/V_T moyen de 32% et le shunt physiologique moyen de 9,5%. On compare dans cet article les résultats ainsi obtenus avec les valeurs publiées pour les patientes enceintes non anesthésiées.

MUTTERBLUT-GASSPANNUNGEN, $(PA_{O_2}-Pa_{O_2})$, PHYSIOLOGISCHE VERSCHIEBUNG UND V_D/V_T WÄHREND ALLGEMEINER NARKOSE BEI KAISERSCHNITT

ZUSAMMENFASSUNG

Die Messungen der mütterlichen Blutgasspannung $(PA_{O_2}-Pa_{O_2})$, die Berechnungen der Pulmonarvenen-Beimischung (physiologische Verschiebung) und des Totraum/Atemvolumen-Verhältnisses (V_D/V_T) wurden bei 14 Patientinnen während eines Kaiserschnitts vorgenommen. Die Messungen wurden nach Einleitung einer allgemeinen Narkose und vor der Geburt vorgenommen—bei nach links geneigten Patientinnen. Bei einer mittleren eingeatmeten Sauerstoffkonzentration von 67,5% betrug der Pa_{O_2}-Mittelwert 44,3 kPa, der $(PA_{O_2}-Pa_{O_2})$-Mittelwert 18,4 kPa der V_D/V_T-Mittelwert 32% und die mittlere physiologische Verschiebung 9,5%. Diese Ergebnisse werden mit veröffentlichten Werten für nicht-narkotisierte schwangere Patientinnen verglichen.

TENSIONES MATERNALES SANGRE-GAS, $(PA_{O_2}-Pa_{O_2})$, DERIVACION FISIOLOGICA Y V_D/V_T DURANTE ANESTESIA GENERAL PARA OPERACION CESAREA

SUMARIO

En 14 pacientes sometidas a una operación cesarea, se efectuaron mediciones de las tensiones maternales sangre-gas $(PA_{O_2}-Pa_{O_2})$ de la mezcla venosa pulmonar calculada (derivación fisiológica) y de la relación del volumen de flujo/espacio muerto (V_D/V_T). Las mediciones se realizaron después de la inducción de la anestesia general y antes del parto, estando las pacientes inclinadas hacia la izquierda. Con una concentración promedia de oxígeno inspirado del 67,5%, el Pa_{O_2} promedio era de 44,3 kPa, el $(PA_{O_2}-Pa_{O_2})$ promedio de 18,4 kPa, el promedio V_D/V_T del 32% y la derivación fisiológica promedia del 9,5%. Se efectúa una comparación de los resultados con los valores publicados para pacientes embarazadas no-anestesiadas.

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HAEMODYNAMIC EFFECTS OF DOPAMINE AND DOPAMINE COMBINED WITH NITROGLYCERIN IN PATIENTS SUBJECTED TO CORONARY BYPASS SURGERY

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SUMMARY

The haemodynamic effects of dopamine and dopamine with nitroglycerin were evaluated in eight patients with coronary heart disease who underwent aortocoronary bypass surgery. The study was performed under anaesthesia and before surgery. Dopamine 8 $\mu g\ kg^{-1}\ min^{-1}$ alone produced a marked increase of the cardiac index from 2.47 to 3.47 litre $min^{-1}\ m^{-2}$ but only small changes in heart rate (from 65 to 68 beat min^{-1}). This improvement in cardiac performance was accompanied by an increase of the mean pulmonary artery pressure from 10.9 to 21.3 mm Hg and in the left ventricular filling pressure from 6.1 to 13.8 mm Hg with unchanged systemic and pulmonary vascular resistance. Mean arterial pressure increased from 72 to 103 mm Hg. Simultaneous infusion of dopamine (8 $\mu g\ kg^{-1}\ min^{-1}$) and nitroglycerin (mean dose 0.5 $\mu g\ kg^{-1}\ min^{-1}$) resulted in a favourable reduction of mean pulmonary artery pressure (from 21.3 to 14.4 mm Hg) and of left ventricular filling pressure (from 13.8 to 7.9 mm Hg). Cardiac index (from 3.47 to 3.34 litre $min^{-1}\ m^{-2}$) and mean arterial pressure (from 103 to 95 mm Hg) were not reduced to the same extent by the addition of nitroglycerin. The combined treatment of dopamine with nitroglycerin seems to be of value in patients with pre-existing high left ventricular filling pressure or with pulmonary hypertension.

A serious sequel of cardiac surgery is cardiovascular failure. Of the many drugs which improve cardiac output, the catecholamines are widely used. The side-effects of catecholamines on heart rate, cardiac rhythm and the peripheral vessels can offset benefits gained from inotropic support. Dopamine is favoured at present for the treatment of low cardiac output states (Bergerovich et al., 1974) because of its unique ability to dilate splanchnic and renal vessels, coupled with inotropic and moderate chronotropic effects. In contrast to other clinically used catecholamines, an increase of left ventricular filling pressure during treatment with dopamine was observed by several authors (Ramdohr et al., 1973; Loeb, Bredakis and Junner, 1977; Schroeder, 1977; Leier et al., 1978). Loeb and others reported that dopamine treatment may be associated with pulmonary oedema.

In patients with coronary heart disease we compared the haemodynamic effects of dopamine alone and in combination with the vasodilator nitroglycerin (glyceryl trinitrate, TNG) which reduces cardiac pre-load and after-load and could be a useful adjunct to dopamine treatment in cardiac failure.

MATERIALS AND METHODS

Eight patients (age range 38–63 yr) with coronary heart disease undergoing coronary artery bypass surgery were studied. The clinical condition of the patients was grade 3 of the American Society of Anesthesiologists classification. Written informed consent was obtained from each patient.

Preoperative treatment included nitrates and β-blockers (last doses 12 h before operation). Six patients had a pre-existing myocardial infarcation; two patients had a history of arterial hypertension.

Premedication was pethidine 1 mg kg^{-1}, promethazine 50 mg and atropine 0.5 mg i.m. 90 min before induction of anaesthesia.

Arterial pressure was measured continuously through an 18-gauge cannula inserted percutaneously to a radial artery and the mean arterial pressure (m.a.p.) obtained. With the aid of continuous e.c.g. and intravascular pressure monitoring, a triple-lumen Swan–Ganz catheter was advanced into the pulmonary artery via the right internal jugular vein. This catheter was used for measuring mean right atrial ($\overline{P}_{RA}$), pulmonary artery ($\overline{P}_{PA}$) and pulmonary wedge ($\overline{P}_{PCW}$) pressures. All pressures were measured using Statham P 23 dB transducers placed at the mid axillary line and were recorded, with e.c.g. lead V_5, on a Hellige EK 21 eight-channel recorder. Heart rate was calculated from e.c.g. Cardiac output

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was measured by the thermodilution technique using a Fischer BN 7206 computer. The temperature curve was monitored on a Servogor-M recorder. Arterial and mixed venous blood-gases were measured using an AVL 938 blood-gas analyser.

From the measured variables the following were derived: cardiac index (CI), stroke volume index (SVI). Total peripheral resistance (TPR), pulmonary vascular resistance (PVR), right and left ventricular stroke work index (RVSWI, LVSWI) were calculated using the formulae:

$$\mathrm{TPR} = \frac{\mathrm{MAP} - \bar{P}_{\mathrm{RA}}}{\mathrm{CO}} \times 80 \ (\mathrm{dyn\ s\ cm^{-5}})$$

$$\mathrm{PVR} = \frac{\bar{P}_{\mathrm{PA}} - \bar{P}_{\mathrm{PCW}}}{\mathrm{CO}} \times 80 \ (\mathrm{dyn\ s\ cm^{-5}})$$

$$\mathrm{RVSWI} = \frac{1.36 \cdot (\bar{P}_{\mathrm{PA}} - \bar{P}_{\mathrm{RA}})}{100} \times \mathrm{SVI} \ (\mathrm{g \cdot m/m^2})$$

$$\mathrm{LVSWI} = \frac{1.36 \cdot (\mathrm{m.a.p.} - \bar{P}_{\mathrm{PCW}})}{100} \times \mathrm{SVI} \ (\mathrm{g \cdot m/m^2})$$

The product of systolic arterial pressure (ASP) and heart rate served as a predictor of the myocardial oxygen consumption (ASP × HR).

After the cannulation procedure anaesthesia was induced with flunitrazepam 0.015 mg kg^{-1} and fentanyl 0.01 mg kg^{-1}. The trachea was intubated with the aid of suxamethonium 1.0 mg kg^{-1}. Thereafter, pancuronium 0.08 mg kg^{-1} was given. The lungs were ventilated with a Draeger Spiromat ($F_{I_{O_2}}$ 1.0).

In a steady state of anaesthesia a series of control measurements of the cardiac output was taken until two consecutive measurements were within 5%. Dopamine was administered i.v. at an infusion rate of 8 μg kg^{-1} min^{-1}. After 3, 5 and 10 min all measurements were repeated. Following this period TNG was added through a central venous line to the dopamine infusion in a dose which restored $\bar{P}_{\mathrm{PCW}}$ close to the control value. TNG solution was prepared by diluting TNG 50 mg (G. Pohl-Boskamp Pharmaceutical Co.) in 500 ml of 5% dextrose solution. The mean dose of TNG was 0.5 μg kg^{-1} min^{-1} (range 25–75 μg min^{-1}). When a new haemodynamic steady state was obtained, all measurements were repeated after 3, 5 and 10 min.

The mean changes obtained at the control and the 10th min of each period are illustrated and were tested for statistical significance using the Wilcoxon test for paired data. Statistical significance was defined as $2\alpha \leq 0.05$. The data are presented as mean ± SEM.

RESULTS

The control values for the haemodynamic variables of the awake and anaesthetized patients are summarized in table I. The cardiac index (fig. 1) increased from 2.47 to 3.47 litre min^{-1}m^{-2} (40%) with dopamine and did not change significantly after the addition of TNG 3.34 litre min^{-1} m^{-2}. The improvement

TABLE I. *Control haemodynamic values in the patients before onset of anaesthesia and during anaesthesia (mean ± SEM)*

	Awake	Anaesthetized
CI (litre min^{-1} m^{-2})	3.34 ± 0.20	2.47 ± 0.15
HR (beat min^{-1})	67 ± 4	65 ± 3
SVI (ml m^{-2})	50.0 ± 2.6	38.0 ± 2.1
M.a.p. (mm Hg)	92 ± 3	72 ± 4
TPR (dyn s cm^{-5})	1123 ± 68	1149 ± 63
$\bar{P}_{\mathrm{PA}}$ (mm Hg)	15.1 ± 1.5	10.9 ± 1.1
PVR (dyn s cm^{-5})	104 ± 14	84 ± 12
$\bar{P}_{\mathrm{RA}}$ (mm Hg)	2.8 ± 0.5	2.7 ± 0.5
$\bar{P}_{\mathrm{PCW}}$ (mm Hg)	7.1 ± 0.9	6.1 ± 0.8
LVSWI (g·m/m^2)	58 ± 4	35 ± 4
RVSWI (g·m/m^2)	8.2 ± 0.6	4.2 ± 0.4
($Ca_{O_2} - C\bar{v}_{O_2}$) (ml dl^{-1})	4.1 ± 0.16	4.7 ± 0.29
ASP·HR	9345 ± 740	6743 ± 425

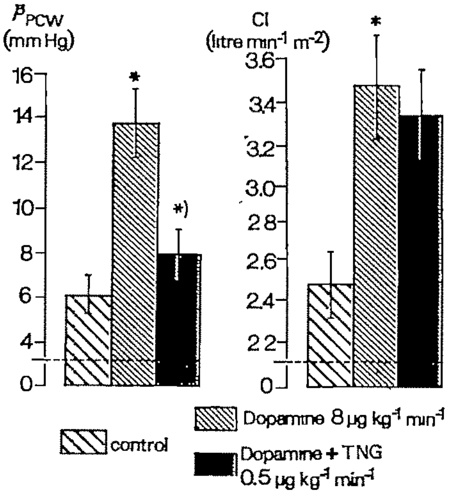


FIG. 1. Mean values (± SEM) for cardiac index (CI) and pulmonary wedge pressure ($\bar{P}_{\mathrm{PCW}}$) during the control period, with dopamine and during the simultaneous infusion of dopamine and TNG ($n = 8$). $2\alpha = 0.05$ * (compared with control); $2\alpha = 0.05$ *) (compared with dopamine alone).

in cardiac performance following the infusion of dopamine was accompanied by an increase in left ventricular filling pressure from 6.1 to 13.8 mm Hg. This returned towards the control value (7.9 mm Hg) when TNG was added.

The heart rate (fig. 2) remained largely unaffected during dopamine infusion and also during the combined administration of dopamine with TNG.

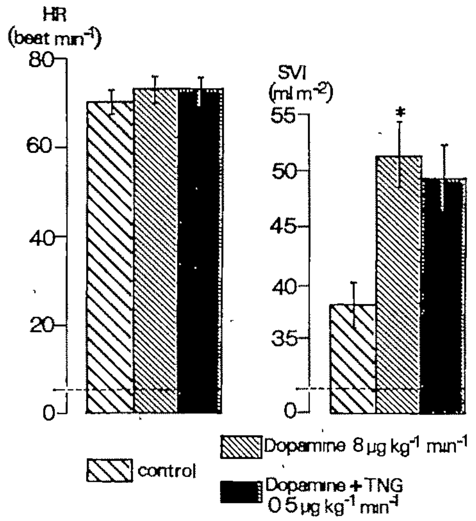


FIG. 2. Mean values (± SEM) for the heart rate (HR) and the stroke volume index (SVI) during the control period, with dopamine and during the simultaneous infusion of dopamine and TNG ($n = 8$). For the significance of the statistical symbols see fig. 1.

Therefore the changes in stroke volume index paralleled those of cardiac index. None of the patients developed cardiac arrhythmia. In two patients an additional increase of pre-existing ST-segment depression (lead V_6) occurred during the administration of dopamine, which was promptly reversed by the addition of TNG.

The mean arterial pressure (fig. 3) was increased by dopamine from 72 to 103 mm Hg and decreased to 95 mm Hg following the administration of TNG. The product of heart rate times systolic arterial pressure, which is an indirect index of myocardial oxygen consumption, increased with dopamine from 6743 to 10 837 and decreased slightly to 10 629 during the combined infusion of dopamine with TNG. However, the dopamine-induced increase in myocardial oxygen demand exceeded the control value (9345) only slightly in the awake patients (table I).

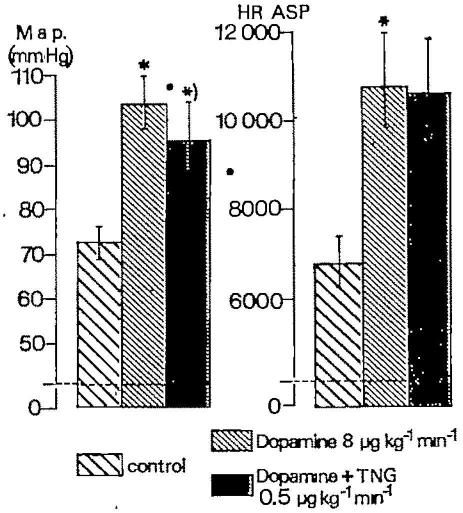


FIG. 3. Mean values (± SEM) for the mean arterial pressure (m.a.p.) and the product of heart rate and systolic arterial pressure (HR·ASP) during the control period, with dopamine and during the simultaneous infusion of dopamine and TNG ($n = 8$). For the significance of the statistical symbols see fig. 1.

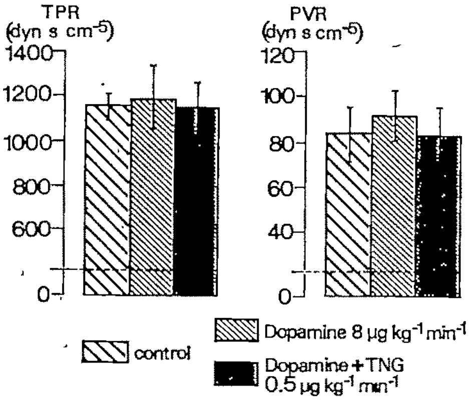
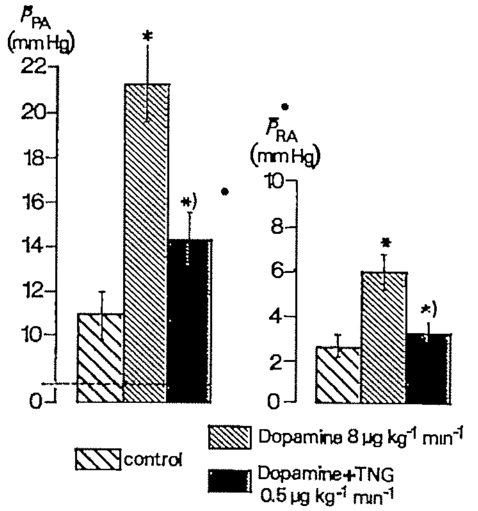


FIG. 4. Mean values (± SEM) for the total peripheral (TPR) and the pulmonary vascular (PVR) resistance during the control period, with dopamine and during the simultaneous infusion of dopamine and TNG ($n = 8$). For the significance of the statistical symbols see fig. 1.

No significant changes in the peripheral and pulmonary vascular resistance (fig. 4) were observed throughout the study.

Dopamine caused a significant increase in the mean pulmonary artery pressure (fig. 5) from 10.9 to 21.3 mm Hg, which returned towards the control value (14.4 mm Hg) when TNG was added. Right



• FIG. 5. Mean values (± SEM) for the mean pulmonary artery pressure ($\bar{P}_{PA}$) and the mean right atrial pressure ($\bar{P}_{RA}$) during the control period, with dopamine and during the simultaneous infusion of dopamine and TNG ($n = 8$). For the significance of the statistical symbols see fig. 1.

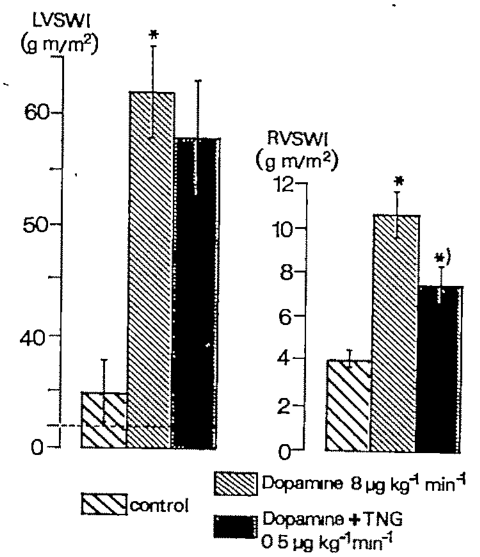


FIG. 6. Mean values (± SEM) for the left ventricular (LVSWI) and right ventricular (RVSWI) stroke work index during the control period, with dopamine and during the simultaneous infusion of dopamine and TNG ($n = 8$). For the significance of the statistical symbols see fig. 1.

atrial pressure was also increased by dopamine and reduced towards the control value by the combined infusion of dopamine with TNG.

The administration of dopamine was associated with an increase in left ventricular stroke work index (85%) which remained unchanged after the addition of TNG (fig. 6). Right ventricular stroke work index increased by 155% with dopamine and by 79% following dopamine and TNG.

The arterial–mixed venous oxygen content difference (fig. 7) was reduced by dopamine (from 4.7 to

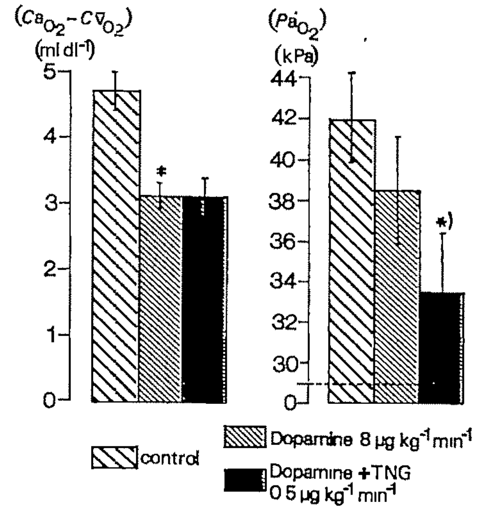


FIG. 7. Mean values (± SEM) for the arterial–mixed venous oxygen content difference ($Ca_{O_2}-C\bar{v}_{O_2}$) and the arterial oxygen tension (Pa_{O_2}) during the control period, with dopamine and during the simultaneous infusion of dopamine and TNG ($n = 8$). For the significance of the statistical symbols see fig. 1.

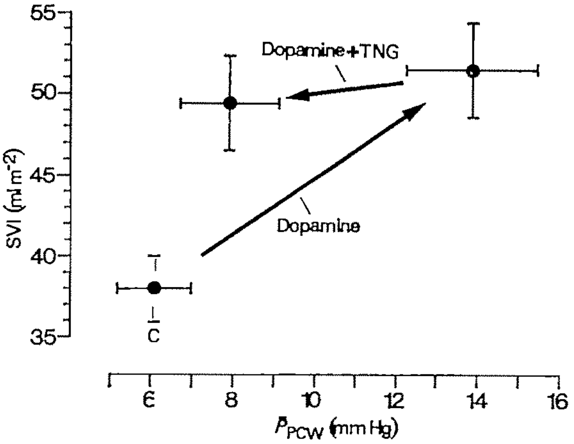


FIG. 8. Left ventricular function plots during the conltro period (C), during dopamine infusion and during the combining administration of dopamine with TNG (means ± SEM, $n = 8$).

3.0 ml dl^{-1}) and did not change with the combined dopamine and TNG infusion. Dopamine produced a reduction in Pa_{O_2} from 42.0 to 38.4 kPa. The addition of TNG resulted in a further decrease of Pa_{O_2} from 38.4 to 33.5 kPa.

In figure 8, stroke volume index on the vertical axis is plotted against pulmonary wedge pressure on the horizontal axis. During dopamine infusion the plot moved upwards and to the right, suggesting an improvement of left ventricular pump function associated with a shift to a greater filling pressure. When TNG was added, the plot moved to the left and only slightly downwards, suggesting no change in the inotropic response with a significant decrease in the increased left ventricular filling pressure.

DISCUSSION

This study was performed under steady-state anaesthesia before the surgical procedure. The control data show that the haemodynamic function of the patients was depressed but not in need of catecholamine support. Nevertheless, we preferred this period of a stable haemodynamic state to determine the specific drug effects. The assessment of pure drug-related haemodynamic changes during the period of emergence from cardiopulmonary bypass is difficult in the presence of changing circulatory status. Periods of ischaemia, hypothermia and direct trauma to the heart, arrhythmia, electrolyte and volume imbalance are some of the possible explanations for this instability. We believe that it is justified to extrapolate our haemodynamic results to many clinical situations following open heart surgery during which inotropic support is necessary.

Some authors (Ramdohr et al., 1973; Loeb, Bredakis and Junner, 1977; Schroeder, 1977) recommend that the dose of dopamine should be limited to 5 $\mu g\ kg^{-1}\ min^{-1}$ because greater infusion rates may be associated with increases of the left ventricular filling pressure which may offset the benefit of inotropic support. On the other hand, several studies (Harrison, Kerber and Aldermann, 1970; Sunder-Plassmann et al., 1974; Goldberg, 1977; Leier et al., 1978) demonstrate that greater doses of dopamine are often necessary to increase cardiac output in patients with severe heart failure. We found dopamine 8 $\mu g\ kg^{-1}\ min^{-1}$ to increase cardiac and stroke index with a concomitant increase in left ventricular filling pressure but without causing vasoconstriction in the systemic and pulmonary vascular beds. The shift of the left ventricular function plot towards greater filling pressures results in an increase of myocardial wall tension and oxygen demand and may provoke myocardial ischaemia or pulmonary congestion. The property of dopamine to exert inotropic effects and to increase the left ventricular filling pressure concomitantly without affecting systemic vascular resistance is specific and not shared by other catecholamines. The increase of pre-load is supposed to be a result of two mechanisms: (1) dopamine induces a blood volume shift from the peripheral to the central circulation by venous constriction (Ramdohr et al., 1973); (2) dopamine reduces the ventricular compliance.

To achieve optimal haemodynamic improvement it seemed reasonable to combine dopamine with nitroglycerin (TNG). Nitroglycerin affects principally the capacitance side of the venous compartment at slower infusion rates (about 0.5 $\mu g\ kg^{-1}\ min^{-1}$). Moreover, TNG has been shown to increase left ventricular compliance (Sauer et al., 1976; Strauer and Scherpe, 1978).

Our data demonstrate that the addition of TNG reduced the increase in left ventricular filling pressure caused by dopamine towards the control values, without markedly affecting mean arterial pressure, systemic vascular resistance, cardiac output and stroke volume. TNG also reduced right ventricular filling pressure and pulmonary artery pressure. Right ventricular stroke work index was significantly reduced whereas the left ventricular stroke work index remained largely unaffected when TNG was added.

Reference was made to dopamine-induced venous admixture by Huckauf, Ramdohr and Schroeder (1974). We also observed a modest decrease of the arterial oxygen tension with dopamine. It appeared that TNG additionally increased venous admixture, since there was a further reduction in arterial Po_2.

In conclusion, the findings of our study demonstrate that TNG prevents an increase in left ventricular filling pressure and wall tension during dopamine treatment without offsetting the principal advantages of dopamine. The beneficial effects of addition of TNG to dopamine may be especially of value in patients with congestive heart failure or pulmonary hypertension, who need inotropic support with dopamine.

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EFFETS HEMODYNAMIQUES DE LA DOPAMINE ET D'UN MELANGE DE DOPAMINE ET DE NITROGLYCERINE CHEZ LES MALADES SOUMIS A UNE INTERVENTION CHIRURGICALE METTANT EN CAUSE UNE DERIVATION CORONAIRE

RESUME

On a procédé à une estimation des effets hémodynamiques de la dopamine et d'un mélange de dopamine et de nitroglycérine sur huit malades souffrant d'une coronaropathie et ayant subi une intervention chirurgicale mettant en cause une dérivation aortocoronarienne. L'étude a été effectuée sous anesthésie et avant l'intervention chirurgicale. La dopamine seule, à raison de 8 μg kg^{-1} min^{-1} a provoqué une augmentation marquée de l'index cardiaque qui est passé de 2,47 à 3,47 litre min^{-1} m^{-2}, mais seulement des changements mineurs dans la fréquence cardiaque (de 65 à 68 battements min^{-1}). Cette amélioration de la performance cardiaque a été accompagnée d'une augmentation de la pression moyenne de l'artère pulmonaire—qui est passée de 10,9 à 21,3 mm Hg—et de la pression de remplissage du ventricule gauche—qui est passée de 6,1 à 13,8 mm Hg—sans qu'il n'y ait aucun changement dans la résistance vasculaire pulmonaire et systémique. La pression artérielle moyenne a augmenté de 72 à 103 mm Hg. L'infusion simultanée de dopamine à raison de 8 μg kg^{-1} min^{-1} et de nitroglycérine (dose moyenne 0,5 μg kg^{-1} min^{-1}) a entraîné une réduction favorable de la pression moyenne de l'artère pulmonaire (de 21,3 à 14,4 mm Hg) et de la pression de remplissage du ventricule gauche (de 13,8 à 7,9 mm Hg). L'index cardiaque (qui est passé de 3,47 à 3,34 litre min^{-1} m^{-2}) et la pression artérielle moyenne (de 103 à 95 mm Hg) n'ont pas été réduits dans les mêmes proportions par l'addition de nitroglycérine. Le traitement combinant dopamine et nitroglycérine semble être valable pour les malades chez lesquels il pré-existe une pression élevée de remplissage du ventricule gauche ou ayant une hypertension pulmonaire.

HÄMODYNAMISCHE WIRKUNGEN VON DOPAMIN UND DOPAMIN-NITROGLYZERIN BEI PATIENTEN MIT OPERATIONEN MIT HERZKREISLAUF-BYPASS

ZUSAMMENFASSUNG

Die hämodynamischen Wirkungen von Dopamin und Dopamin-Nitroglyzerin wurden bei acht Patienten mit Herzkreislauferkrankungen bewertet, die Eingriffen mit Aorta-Bypass unterzogen wurden. Die Studie wurde unter Narkose und vor dem Eingriff durchgeführt. Dopamin (8 μg kg^{-1} min^{-1}) allein bewirkte ein deutliches Ansteigen des Herzindex von von 2,47 auf 3,47 Liter min^{-1} m^{-2}, aber nur kleine Änderungen des Herzminutenvolumens von 65 auf 68 Schläge/min^{-1}. Diese Herzleistungsverbesserung war begleitet von einem Anstieg des mittleren Lungenarteriendruckes von 10,9 auf 21,3 mm Hg, und des linksventrikularen Fulldruckes von 6,1 auf 13,8 mmHg mit unverändertem sytemischen und Lungengefässwiderstand. Der mittlere arterielle Druck stieg von 72 auf 103 mm Hg. Gleichzeitige Infusion von 8 μg kg^{-1} min^{-1} und von 0,5 μg kg^{-1} min^{-1} Nitroglyzerin bewirkte eine gunstige Reduktion des mittleren Lungenarteriendruckes (von 21,3 auf 14,4 mmHg) und des linksventrikularen Fülldruckes (von 13,8 auf 7,9 mmHg). Durch die Beigabe von Nitroglyzerin nicht im selben Ausmass reduziert wurden der Herzindex (von 3,47 auf 3,34 Liter min^{-1} m^{-2}) und der mittlere arterielle Druck (von 103 auf 95 mm Hg). Die Behandlung mit einer Kombination von Dopamin und Nitroglyzerin scheint fur Patienten mit vorhandenem hohen linksventrikularen Fülldruck oder mit Lungenhypertension von Wert zu sein.

EFECTOS HEMODINAMICOS DE LA DOPAMINA Y DE DOPAMINA COMBINADA CON NITROGLICERINA EN PACIENTS SOMETIDOS A CIRUJIA DE DESVIACION CORONARIA

SUMARIO

Se evaluaron los efectos hemodinámicos de la dopamina y de dopamina con nitroglicerina en ocho pacientes padeciendo de enfermedades coronarias que fueron sometidos a una operación quirúrgica de desviación aortocoronaria. Se llevó a cabo el estudio bajo anestesia y antes de la operción. Con dopamina 8 μg kg^{-1} min^{-1} sólo, se registró un aumento marcado del índice cárdiaco, de 2,47 a 3,47 litro

min^{-1} m^{-2}, pero pequeñas alteraciones únicamente en el ritmo cárdiaco (de 65 a 68 latidos min^{-1}). Esta mejoría de la función cárdiaca se acompanó de un aumento de la presión de un aumento de la presión media de la arteria pulmonar, de 10,9 a 21,3 mm Hg, y de la presión de relleno ventricular izquierda de 6,1 a 13,8 mm Hg, con una resistencia vascular pulmonar y sistémica inalterada. La presión arterial media aumentó de 72 a 102 mm Hg. Una infusión simultánea de 8 μg kg^{-1} min^{-1} de dopamina con nitroglicerina (dosis media de 0,5 μg kg^{-1} min^{-1}) dió por resultado una reducción favorable de la presión media de la arteria pulmonar (de 21,3 a 14,4 mm Hg) ye de la presión de relleno ventricular izquierda (de 13,8 a 7,9 mm Hg). El índice cárdiaco (de 3,47 a 3,34 litro min^{-1} m^{-2}) y la presión arterial media (de 103 a 95 mm Hg) no disminuyeron del mismo modo al añadirle la nitroglicerina. El tratamiento combinado de dopamina con nitroglicerina parece ser valioso en pacientes con alta presión de relleno ventricular izquierda o con hipertensión pulmonar.

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CARDIOVASCULAR RESPONSE TO THE I.V. ADMINISTRATION OF MORPHINE IN CRITICALLY ILL PATIENTS UNDERGOING IPPV

J. J. ROUBY, P. GLASER, G. SIMMONEAU, G. GORY, R. GUESDE AND P. VIARS

SUMMARY

The haemodynamic changes following the administration of morphine 0.15 and 0.30 mg kg^{-1} i.v. were studied in 11 patients, free from known cardiac disease. All patients were acutely ill and their lungs were being ventilated mechanically. In those patients receiving 0.15 mg kg^{-1}, the only haemodynamic change was a slight and transitory decrease in the systolic arterial pressure. In contrast, several changes were observed in patients receiving 0.30 mg kg^{-1}: an immediate and prolonged decrease in the cardiac index was noted along with transient decreases in heart rate, stroke volume index, arterial pressure and left stroke work index. These results suggest that the haemodynamic cost of morphine 10 mg is negligible but could be significant when 20 mg has been administered and must be weighed against its beneficial effects in the critically ill patient.

Morphine has been used widely in cardiology in the treatment of myocardial infarction and cardiogenic pulmonary oedema, and is being used increasingly in anaesthesia and in intensive care units, where it permits adaptation to mechanical ventilation of certain acutely ill patients whose ventilation is difficult to control. However, as the majority of the haemodynamic studies of morphine discuss spontaneously breathing patients with heart disease, the present study evaluated the haemodynamic effects of the administration of morphine 0.15 and 0.30 mg kg^{-1} i.v. in 11 artificially ventilated, acutely ill patients free of known cardiac disease.

METHODS

Table I shows the clinical and haemodynamic data for the 11 patients studied who were selected according to the following criteria:

No cardiac disease, stable sinus rhythm and stable haemodynamic condition.

No psychotropic treatment during the 3 days preceding the investigation.

Intermittent positive pressure ventilation with adaptation to the ventilator before the administration of morphine (stable Pa_{CO_2} during the investigation).

A total of 14 haemodynamic studies were carried out. These were divided into two groups: the first group consisted of seven studies made on seven patients who received morphine hydrochloride 0.30 mg kg^{-1} i.v. over 2 min. The second group consisted of seven haemodynamic studies made on four other patients and also on three patients from the previous group. Each received morphine 0.15 mg kg^{-1} administered similarly. The three patients who had two haemodynamic studies received, on the first day, morphine 0.30 mg kg^{-1} and, 24 h later, morphine 0.15 mg kg^{-1}.

Two days before each haemodynamic study, arterial and thermistor-tipped Swan–Ganz catheters were inserted as an integral part of patient care. When a stable haemodynamic condition was obtained, data were recorded, both before the injection of morphine and 5, 15, 30, 60 and 90 min afterwards. Cardiac output was measured in triplicate by the thermodilution method (Edwards apparatus No. 9500) after injection of 10 ml of isotonic glucose at 0 °C into the right atrium. Central venous pressure (c.v.p.), mean pulmonary arterial pressure (MPAP), pulmonary wedge pressure (PWP) and systolic, diastolic and mean aortic pressures (SAP, DAP, MAP) were monitored using Statham P23 transducers connected to the arterial and Swan–Ganz catheters. From these measured data, the following were calculated:

$$\text{Total vascular resistance (TVR)} = \frac{\text{MAP} - \text{CVP}}{\dot{Q}_t}$$
(units of resistance)

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TABLE I. *Initial clinical and haemodynamic data for the* 11 *patients. CI = cardiac index (litre* min^{-1} m^{-2}*); HR = heart rate (beat* min^{-1}*); PWP = pulmonary wedge pressure (mm Hg); MAP = mean aortic pressure (mm Hg); D = dead; S = survived.* **The patient underwent two haemodynamic studies; on the first day morphine was injected at a dose of* 0.30 *mg* kg^{-1} *and* 24 *h later, at a dose of* 0.15 *mg* kg^{-1}*; the two readings refer to the basic state before each study*

Patient	Age (yr)	Sex	Diagnosis	Outcome	Temp. (°C)	CI	HR	PWP	MAP	Pa_{CO_2} (kPa)
1	52	F	Multiple injuries Diaphragmatic hernia	D	39	4.1	129	8	93	4.4
2	44	M	Multiple injuries Flail chest Acute renal failure	D	38	5.3	76	15	120	4.8
3	64	F	Multiple injuries Flail chest Pulmonary contusion	D	38	3.5	120	10	98	4.3
4	36	M	Multiple injuries Cerebral contusion	S	37	4.1	68	14	97	4.5
5	65	M	Multiple injuries Flail chest	D	38	4.9	100	9	80	4.5
6	22	M	Multiple injuries Cerebral contusion	S	39	5.5	102	4	115	4.3
7	59	M	Multiple injuries Flail chest Pulmonary contusion	D	37	3.3	91	10	100	4.7
8	41	F	Right hepatectomy for hydatid cyst	D	39	4.5	140	6	79	4.8
9*	30	M	Multiple injuries	S	37	3.7	95	3	90	4.9
			Fracture of the lumbar rachis		38	3.5	109	10	90	4.8
10*	32	M	Multiple injuries	S	37	4.3	107	8	88	4.3
			Cerebral contusion		38	4.2	100	9	88	4.5
11*	29	M	Multiple injuries	S	37	4.6	115	3	110	4.4
			Cerebral contusion		38	4	80	10	97	4.7

Pulmonary vascular resistance (PVR) =
(units of resistance)

$$\frac{MPAP-PWP}{Q_t}$$

Stroke volume index (SVI) = $\frac{CI}{HR}$
($ml\ m^{-2}$)

Left stroke work index (LSWI) =
($g\ m^{-2}$) $13.6(MAP-PWP)\times SVI$

where Q_t = cardiac output
CI = cardiac index

Statistical analysis of data collected during the investigation was performed using the paired Student's *t* test, each patient acting as his own control.

RESULTS

Morphine 0.15 *mg* kg^{-1} *(table II)*

A remarkable stability in the haemodynamic data was seen. Systolic arterial pressure alone decreased significantly in the first 15 min compared with control values. However, this decrease was transitory and was not marked.

Morphine 0.3 mg kg^{-1} *(table III)*

In contrast to the previous group, several variations in the haemodynamic patterns were observed. There was an immediate and prolonged decrease in the cardiac index following the administration of morphine. This change was significant throughout the study. Simultaneously, both heart rate and stroke volume index were decreased significantly during the 1st h (fig. 1).

An immediate decrease in the mean aortic pressure was seen also. This was transitory and of moderate degree, reaching only 10% by the 5th min, and was accompanied by a gradual but non-significant increase

TABLE II. *Haemodynamic effects (mean ± SD) before (control) and after morphine* 0.15 *mg kg*$^{-1}$ *i.v. in seven subjects without demonstrable heart disease.* $*P < 0.05$; $**P < 0.01$; $***P < 0.001$

	Control	5 min	15 min	30 min	60 min	90 min
Heart rate	104	102	101	101	103	103
(beat min^{-1})	±22	±22	±23	±23	±24	±24
		n.s.	n.s.	n.s.	n.s.	n.s.
Systolic arterial pressure	145	129	138	147	156	154
(mm Hg)	±28	±30	±36	±50	±56	±48
		**	*	n.s.	n.s.	n.s.
Diastolic arterial pressure	79	75	77	78	82	81
(mm Hg)	±12	±5	±7	±12	±11	±11
Mean arterial pressure	94	88	93	94	95	97
(mm Hg)	±13	±7	±11	±16	±13	±17
Cardiac index	4.1	4.1	4	4.2	4.1	4.2
(litre m^{-1} m^{-2})	±0.6	±0.5	±0.7	±0.7	±0.5	±0.6
Stroke volume index	41	44	42	44	42	42
(ml m^{-2})	±13	±13	±13	±14	±11	±11
Left stroke work index	49	45	49	52	50	51
(g m^{-2})	±23	±14	±20	±25	±18	±21
Total vascular resistance	13	12	13	13	13	13
(units of resistance)	±2	±2	±3	±3	±3	±3
Pulmonary vascular resistance	1.5	1.4	1.4	1.4	1.4	1.4
(units of resistance)	±0.4	±0.4	±0.4	±0.3	±0.5	±0.3
Central venous pressure	7.5	7.8	7.9	7.4	7.5	8.1
(mm Hg)	±2.5	±2	±2.5	±2.5	±3	±3.5
Mean pulmonary arterial pressure	21	20	21	20	20	20
(mm Hg)	±4	±5	±4.5	±5	±4.5	±4
Pulmonary wedge pressure	10	10	11	10	10	10
(mm Hg)	±2.5	±2.5	±3	±3	±3.5	±3

TABLE III. *Haemodynamic effects (mean ± SD) before (control) and after morphine* 0.30 *mg kg*$^{-1}$ *i.v. in seven subjects without demonstrable heart disease.* $*P < 0.05$; $**P < 0.01$; $***P < 0.001$

	Control	5 min	15 min	30 min	60 min	90 min
Heart rate	98	90	90	86	88	90
(beat min^{-1})	±18	±19	±20	±19	±20	±20
		*	*			
Systolic arterial pressure	141	126	130	131	137	145
(mm Hg)	±17	±15	±17	±24	±26	±29
		**	*			
Diastolic arterial pressure	80	78	80	80	79	82
(mm Hg)	±11	±11	±10	±11	±9	±14
Mean arterial pressure	97	88	89	91	92	94
(mm Hg)	±11	±8	±9	±13	±11	±10
		**	**			
Cardiac index	4.3	3.8	3.6	3.5	3.5	3.9
(litre min^{-1} m^{-2})	±0.6	±0.7	±0.7	±0.5	±0.5	±0.6
		***	**	**	**	*
Stroke volume index	53	45	42	43	42	46
(ml m^{-2})	±11	±14	±13	±12	±11	±12
			*	*	*	
Left stroke work index	55	48	46	49	48	54
(g m^{-2})	±14	±17	±17	±17	±16	±17
		*	**			
Total vascular resistance	12	12	13	13.9	14	12.9
(units of resistance)	±2.5	±2.8	±2.7	±3	±3.4	±3
Pulmonary vascular resistance	1.5	1.6	1.6	1.8	1.7	1.6
(units of resistance)	±0.9	±1	±0.8	±0.9	±0.6	±0.8
Central venous pressure	6.5	6.9	7.8	7.5	8	7.7
(mm Hg)	±3.4	±2.9	±3.5	±3.6	±3.5	±3.6
Mean pulmonary arterial pressure	18	19	20	20	20	20
(mm Hg)	±5.2	±5.8	±4	±5	±4.5	±5
Pulmonary wedge pressure	8	9.5	10	9.2	9.3	8.9
(mm Hg)	±4.5	±4	±4	±4.3	±3.9	±4.1

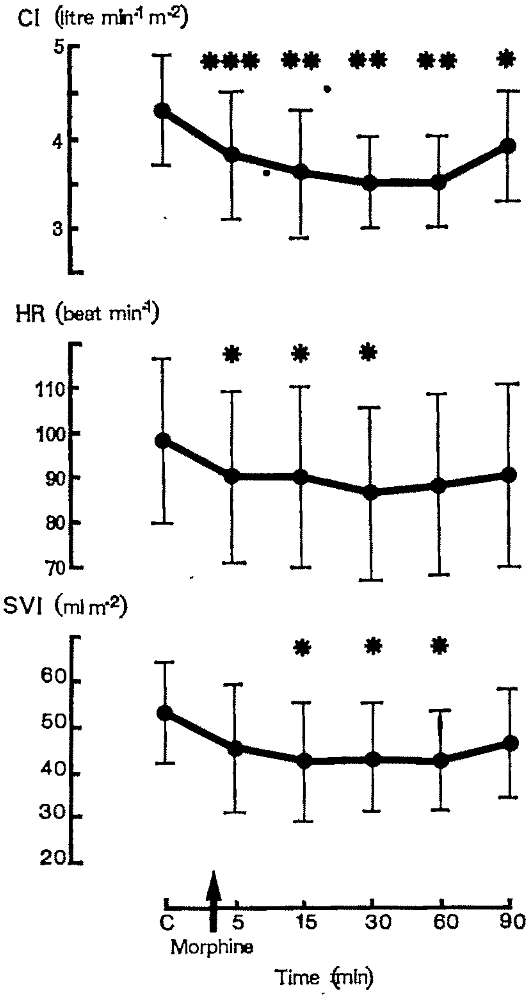

FIG. 1. Effects of morphine 0.30 mg kg^{-1} i.v. on cardiac index (CI), heart rate (HR), and stroke volume index (SVI) (mean ± SD). *$P<0.05$; **$P<0.01$; ***$P<0.001$.

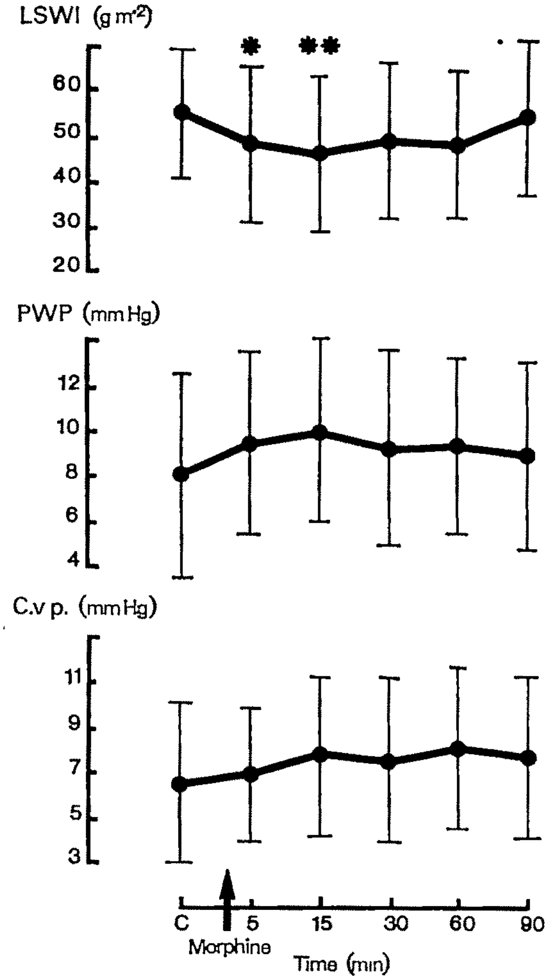

FIG. 2. Effects of morphine 0.30 mg kg^{-1} i.v. on left stroke work index (LSWI), pulmonary wedge pressure (PWP) and central venous pressure (c.v.p.) (mean ± SD). *$P<0.05$; **$P<0.01$.

in the total vascular resistance. No serious hypotensive incident occurred during the administration of morphine.

The left stroke work index was decreased also, but this change was transitory, being significant during the first 15 min only, and was accompanied by insignificant increases in the right and the left cardiac filling pressures (fig. 2).

DISCUSSION

Although several haemodynamic studies have dealt with the effects of the i.v. administration of morphine at doses of about 10 mg, the majority have dealt with spontaneously breathing patients with heart disease. With this dose the only haemodynamic change observed usually was a slight decrease in arterial pressure whether in cardiac patients (Thomas et al., 1965; Grendhal, Andersen and Muller, 1973) or in patients convalescing from multiple injuries (Samuel, Clarke and Dundee, 1977). Our study confirms the previously published data on this point in that, after the injection of morphine 0.15 mg kg^{-1} there was transitory arterial hypotension which affected only the systolic arterial pressure, but both systolic and mean arterial pressure were affected at a dose of 0.30 mg kg^{-1}. Nevertheless, the hypotension was moderate and none of the 11 patients studied suffered a severe hypotensive incident with a systolic arterial pressure less than 100 mm Hg. Although the production of arterial hypotension is no longer in question, the mechanism of its induction is. Even if morphine-induced histamine release has been established in animals (Thompson and Walton, 1966) its role seems to be negligible in man (Zelis et al., 1974). The mechanism by which morphine, administered in the usual doses, induces arterial hypotension seems to be that of a reflex reduction in sympathetic alpha-adrenergic tone at a central nervous system level, as the studies by Zelis and co-workers (1974, 1977) have shown on the isolated human arm. It must be recognized, however, that haemodynamic studies on the administration of morphine in the usual dose (<0.5 mg kg^{-1}) have not, for the most part, indicated a significant decrease in the total vascular resistance (Thomas et al., 1965; Alderman et al., 1972; Grendhal, Andersen and Muller, 1973; Lee et al., 1976). In fact, such a decrease has been reported after the administration of large i.v. doses of morphine (1–3 mg kg^{-1}) by Lowenstein and colleagues (1969), Stoelting and Gibbs (1973) and Wong and co-workers (1973). In our study, the total vascular resistance was unchanged at a dose of 0.15 mg kg^{-1} and increased after administration of morphine 0.30 mg kg^{-1}. However, this small increase was insufficient to counteract completely the effects of the decrease in cardiac output on arterial pressure. However, interpretation of the calculated total vascular resistance would seem to us to be difficult, especially when it involves the detection of slight variations in vasomotor tone associated with changes in cardiac output.

The haemodynamic studies of morphine have noted variable and unpredictable effects of the drug on the cardiac index; decreases (Alderman et al., 1972; Lappas et al., 1975), increases (Lowenstein et al., 1969; Stoelting and Gibbs, 1973; Wong et al., 1973), and no change (Grendhal, Andersen and Muller, 1973; Lappas et al., 1975; Lee et al., 1976) having been reported. In subjects free of cardiac disease, remarkable stability has been seen whether the dose be 1 mg kg^{-1} (Lowenstein et al., 1969) or 0.15 mg kg^{-1} (Samuel, Clarke and Dundee, 1977). Our study has confirmed a similar stability in the cardiac index at a dose of 0.15 mg kg^{-1}, but has shown a significant and prolonged decrease in the cardiac index at a dose of 0.30 mg kg^{-1}. It is known that, in most instances, acutely ill patients have an increased oxygen consumption and that morphine can diminish this by virtue of its central sedative activity (Fejfar et al., 1957; Alderman et al., 1972; Grendhal, Andersen and Muller, 1973). This mechanism probably plays an important part in the decrease in cardiac index observed in our seven patients who received morphine 0.30 mg kg^{-1}. However, this has still to be proved, since oxygen consumption was not measured in this study. On the other hand, the decrease in the heart rate seen in this study cannot explain the decrease in the cardiac index since the stroke volume index decreased significantly. Another hypothesis which might explain the decrease in cardiac output is that there may be a decrease in venous return resulting from the administration of the morphine. Numerous studies, including those by Zelis and colleagues (1974), Samuel, Unni and Dundee (1977) and Vismara, Leaman and Zelis (1976), have shown that morphine produces an increase in the peripheral venous capacitance, but in our study, after administration of morphine 0.30 mg kg^{-1}, such a decrease in venous return is doubtful considering that there was no decrease in the cardiac filling pressures associated with the decrease in the stroke volume index. Moreover, a tendency to an increase in the cardiac filling pressures was seen, supporting other studies (Lowenstein et al., 1969; Grendhal, Andersen and Muller, 1973; Stoelting and Gibbs, 1973; Wong et al., 1973; Lappas et al., 1975; Lee et al., 1976). This fact, in association with the decrease in cardiac index, could suggest a negative inotropic effect of morphine, but the body of the clinical and experimental studies (Vasko et al., 1966; Pur-Shahriari et al., 1967; Strauer, 1972; Vatner, Marsh and Swain, 1975; Urthaler, Walker and James, 1976) does not support this hypothesis. Another hypothesis explaining the tendency to an increase in cardiac filling pressures could be a morphine-induced modification of the respiratory mechanics and its repercussions on the intrapleural pressure. Morphine is known to decrease thoraco-pulmonary compliance, first by bronchoconstriction, and later by the muscular rigidity that it may induce (Freund et al., 1973). In this way, although it remains to be proved, morphine may produce an increase in measured pulmonary wedge pressure which would no longer reflect exactly the left ventricular filling pressure.

In conclusion, morphine is useful in intensive care by virtue of its depressant effect on ventilation, which facilitates adaptation to the ventilator in patients whose breathing is difficult to control. Apart from its analgesic effect, its non-hypnotic sedative effect is useful in diminishing the anxiety of acutely ill patients. These advantages are obtained at moderate haemodynamic cost: at a dose of 0.15 mg kg^{-1} the only haemodynamic change was a slight decrease in systolic arterial pressure; at a dose of 0.30 mg kg^{-1} decreases in the cardiac index and the left ventricular work index were associated with a slight decrease in diastolic and mean arterial pressures.

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REACTION CARDIOVASCULAIRE A L'ADMINISTRATION INTRAVEINEUSE DE MORPHINE CHEZ LES PERSONNES TRES GRAVEMENT MALADES ET SOUMISES A UNE VENTILATION AU MOYEN DE RESPIRATEURS A PRESSION POSITIVE INTERMITTENTE

RESUME

Les variations hémodynamiques qui se produisent après l'administration intraveineuse de morphine, à raison de 0,15 et de 0,30 mg kg^{-1}, ont été observées sur 11 malades, ne souffrant apparemment d'aucune maladie cardiaque. Toutes ces personnes étaient gravement malades et leurs poumons étaient ventilés par des moyens mécaniques. Chez les malades auxquels on a administré la dose de 0,15 mg kg^{-1}, la seule variation hémodynamique que l'on ait constatée est une diminution légère et transitoire de la pression artérielle systolique. Par contre, on a observé plusieurs variations chez les malades ayant reçu 0,30 mg kg^{-1}: une diminution immédiate et prolongée de l'indice cardiaque en même temps qu'une augmentation transitoire de la fréquence cardiaque, de l'indice du volume systolique, de la pression artérielle et de l'indice du travail cardiaque gauche. Ces résultats laissent penser que la valeur hémodynamique de la morphine à 10 mg est négligeable, mais qu'elle pourrait avoir une certaine importance lorsqu'on en administre 20 mg, et il faut la comparer aux effets bénéfiques qu'elle a sur les personnes très gravement malades.

KARDIOVASKULÄRE REAKTION AUF INTRAVENÖSE VERABREICHUNG VON MORPHIUM BEI SCHWERKRANKEN PATIENTEN UNTER IPPV

ZUSAMMENFASSUNG

Die hämodynamischen Veränderungen nach intravenöser Verabreichung von 0,15 und 0,30 mg kg^{-1} Morphium wurden bei 11 nicht herzkranken Patienten studiert. Sie alle waren akut krank, mit mechanisch belufteten Lungen. Bei den Patienten mit der Dosis 0,15 mg kg^{-1} Morphium bestand die einzige hamodynamische Veränderung in einer leichten und vorubergehenden Senkung des systolischen arteriellen Druckes. Bei Patienten dagegen mit der Dosis 0,30 mg kg^{-1} wurden folgende Veränderungen beobachtet: sofortige und langanhaltende Senkung des Herzindex, zusammen mit vorübergehenden Senkungen des Herzminutenvolumens, des Herzschlagvolumens, des arteriellen Druckes und des linksseitigen Schlagindex. Daher also sind 10 mg Morphium hämodynamisch unwesentlich, nicht aber 20 mg, und dies muss gegen die nützlichen Wirkungen bei schwerkranken Patienten abgewogen werden.

RESPUESTA CARDIOVASCULAR A LA ADMINISTRACION I.V. DE MORFINA EN PACIENTES CRITICOS SOMETIDOS A IPPV

SUMARIO

Se estudiaron los cambios hemodinámicos resultando de la administración de 0,15 y 0,30 mg kg^{-1} de morfina i.v. en 11 pacientes, libres de todo trastorno cárdiaco conocido. Todos los pacientes eran críticamente enfermos y sus pulmones estaban bajo ventilación mecánica. En los pacientes a los cuales se administró 0,15 mg kg^{-1}, el único cambio hemodinámico registrado fue una ligera y transitoria disminución de la presión arterial sistólica. En cambio, en los pacientes que recibieron 0,30 mg kg^{-1}, se observaron varios cambios: se notó una disminución inmediata y prolongada del índice cárdiaco, junto con descensos pasajeros del ritmo cárdiaco, del índice de descarga sistólica, de la presión arterial y del índice de la función sistólica izquierda. Estos resultados hacen pensar que, con 10 mg de morfina, el efecto hemodinámico es insignificante, pero que con la administración de 20 mg, puede ser apreciable, y debe evaluarse en relación con sus efectos beneficiosos en pacientes en estado crítico.

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CARDIORESPIRATORY EFFECTS OF THE SITTING POSITION IN NEUROSURGERY

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SUMMARY

The cardiorespiratory effects of raising patients from the supine to the sitting position for neurosurgery were investigated. The change caused marked decreases in cardiac index, stroke volume, Pa_{O_2} and $\dot{Q}s/\dot{Q}t$, with a significant increase in $(PA_{O_2}-Pa_{O_2})$ and total peripheral resistance. It is concluded that patients who maintain normotension in the sitting position do not necessarily have an adequate circulatory status.

Although the sitting position for neurosurgical operations has always been controversial (Millar, 1972), this position is used occasionally in the Dundee Neurosurgical Unit. As there is little data on the acute cardiorespiratory changes that may occur when a patient is raised from the supine to the sitting position, we investigated these changes.

PATIENTS AND METHODS

Six male patients, free from respiratory or cardiac disease, with ages ranging from 50 to 62 yr, were investigated. Three underwent cervical laminectomy and three division of the trigeminal nerve.

The patients were pre-medicated, 1 h before surgery, with papaveretum 15 mg and atropine 0.6 mg i.m. and anaesthesia was induced with thiopentone 250–300 mg and fentanyl 0.1 mg. Pancuronium 6 mg was administered to produce neuromuscular blockade. The larynx was sprayed with 4 ml of 4% lignocaine, and after intubation of the trachea the lungs were ventilated with 60% nitrous oxide in oxygen using a Cape Waine ventilator. FI_{O_2} was 0.4, sampled about 5 cm above the carina (Servomex oxygen analyser). Anaesthesia was supplemented every 30 min with increments of fentanyl 0.5 mg and pancuronium 2 mg.

After the induction of anaesthesia a Teflon cannula was inserted to the radial artery. A catheter was inserted to the right atrium and its position was confirmed by x-ray. The zero point for the arterial and atrial pressures was the level of the right atrium, taken as the mid-axillary line in the supine position, and the fourth interspace anteriorly in the sitting position.

Arterial pressure and right atrial pressure were obtained from the intra-arterial and central venous cannulae respectively (Bell and Howell transducers). The electrocardiograph was monitored continuously and heart rate obtained. These measurements were displayed on a heated stylus recorder (Devices MX4). Cardiac output was determined with a dye-dilution method utilizing a Waters DR702 cardiac output computer.

Arterial and mixed venous Po_2, Pco_2 and pH were obtained from suitably calibrated electrodes (IL 313) and the results were corrected for any temperature difference between the patient and the electrode system. The haemoglobin and oxygen saturations were measured with an IL 182 co-oximeter.

The oxygen content was calculated from:

$$O_2 \text{ content (ml dl}^{-1}) = \text{Hb} \times 1.39 \times Sa_{O_2} + 0.003 \times Pa_{O_2}$$

(Hb = haemoglobin concentration (g dl^{-1}); Pa_{O_2} is expressed in mm Hg).

PA_{O_2} was calculated using the ideal alveolar air equation:

$$PA_{O_2} = PI_{O_2} - PA_{CO_2}\left(\frac{PI_{O_2}-PE_{O_2}}{PE_{CO_2}}\right)$$

(Nunn, 1963).

$\dot{Q}s/\dot{Q}t$ was calculated from:

$$\dot{Q}s/\dot{Q}t = \frac{Cc'_{O_2}-Ca_{O_2}}{Cc'_{O_2}-C\bar{v}_{O_2}} \times 100$$

After anaesthesia was stabilized in the supine position, cardiac output was measured at 5-min

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intervals for 15 min. After the 15-min period, arterial and mixed venous blood samples were obtained. The mixed venous samples were taken from the right ventricle in two of the patients and from the right atrium in the other four patients. The samples of mixed venous blood were taken in duplicate and the results averaged.

After bandaging the legs from the toes to the groin, the patients were raised slowly into the sitting position over a 10-min period while the arterial pressure was recorded continuously. In the sitting position the patient's legs were elevated to about 3–5° above the horizontal. After 5 min in the sitting position, cardiac output was measured again at 5-min intervals for 15 min. Immediately after the last cardiac output measurement, arterial and mixed venous blood samples were obtained.

Mean values were calculated from the measurements obtained of the individual patient's cardiac index, stroke volume, c.v.p. and mean arterial pressure in both the sitting and the supine positions. These results were then analysed using the two-tailed Student's *t* test.

RESULTS

The change from the supine to the sitting position caused marked decreases in cardiac index, c.v.p., stroke volume, Pa_{O_2} and Qs/Qt ratio. There were significant increases in ($PA_{O_2}-Pa_{O_2}$) and the total peripheral resistance (table I).

DISCUSSION

Although the sitting position is associated with two main problems—hypotension and air embolism—there was no evidence of either of these complications in any of the patients studied. As superior operating conditions are obtained with IPPV as opposed to spontaneous breathing, the former is used with the sitting position in the Dundee Neurosurgical Unit (Martin, 1970), despite a reported increase in the risk of air embolism (Hunter, 1962). Although the mean arterial pressures were maintained in all these patients after the change from supine to sitting position, both the cardiac index and stroke volumes were decreased markedly. The right atrial pressure decreased markedly after the change in position and this may reflect a similar decrease in left atrial pressure.

In all these patients, the change from the supine to the sitting position resulted in a decrease in cardiac output, a low pre-load to the myocardium and a high total peripheral resistance. This is similar to the circulatory changes that occur in the hypovolaemic but normotensive patient. Although bandaging the legs from toes to groin did not prevent the circulatory changes, the use of a G-suit may help to maintain cardiac output in these circumstances.

TABLE I. *Measurements in six patients (mean and SD). t = two-tailed Student's t test*

		Time							
		Supine			Sitting			Supine *v.* sitting	
		5 min	10 min	15 min	30 min	35 min	40 min	*t*	*P*
Cardiac index	$\bar{x}$	3.805	3.785	2.765	2.430	2.436	2.443	3.082	<0.05
(litre m^{-2} min^{-1})	SD	1.010	1.008	1.006	0.703	0.702	0.701		
Stroke volume	$\bar{x}$	80.00	79.0	78.00	50.31	51.157	51.157	3.770	<0.06
(ml)	SD	24.800	24.811	24.208	14.602	14.661	14.661		
Cardiac rate	$\bar{x}$	77.5	77.5	77.5	75.00	75.00	75.00	1.464	<0.25
(beat min^{-1})	SD	10.85	10.84	10.84	8.367	8.367	8.367		
Central venous pressure	$\bar{x}$	4.167	4.167	4.167	−2.833	−2.833	−2.833	6.22	<0.01
(cm H_2O)	SD	1.472	1.472	1.472	2.787	2.787	2.787		
Mean arterial pressure	$\bar{x}$	112.4	112.4	112.4	93.4	108.4	108.4	1.171	>0.25
(mm Hg)	SD	24.4	24.4	24.4	20.6	20.6	20.6		
Total peripheral resistance	$\bar{x}$	1970	2025	2071	3112	3080	3040	3.57	<0.02
(dyne s cm^{-5})	SD	768	753	741	1180	1167	1143		
Pa_{O_2}	$\bar{x}$			20.21			18.62	15.356	<0.001
(kPa)	SD			5.667			5.577		
Pa_{CO_2}	$\bar{x}$			4.153			4.189	1.512	<0.1
(kPa)	SD			0.249			0.275		
($PA_{O_2}-Pa_{O_2}$)	$\bar{x}$			13.343			14.918	13.56	<0.001
(kPa)	SD			5.677			5.547		
Qs/Qt	$\bar{x}$			14.00			10.00	2.84	<0.05
(%)	SD			9.03			6.53		

Although there were marked decreases in cardiac output and stroke volume, a compensatory tachycardia did not develop. This may be because fentanyl has a vagotonic effect on the myocardium (Freye, 1974; Wen-Shri et al., 1976).

Using the same minute and tidal volume in each patient after the change to the sitting position, there were no changes in Pa_{CO_2}. Although an accurate measurement of physiological deadspace was not made, it is probable that large changes did not occur. However, there were marked decreases in Pa_{O_2} when the patients were raised to the sitting position. As FI_{O_2} was maintained constant and as $\dot{Q}s/\dot{Q}t$ decreased after elevation to the sitting position, the decrease in the Pa_{O_2} appeared to be a result of the decrease in cardiac output. Although there was a decrease in $\dot{Q}s/\dot{Q}t$ which occurs with a reduced cardiac output (Smith, Cheney and Winter, 1973), the decrease in $\dot{Q}s/\dot{Q}t$ did not compensate to maintain normal arterial oxygenation. Increasing the inspired oxygen concentration may marginally increase Pa_{O_2} of the blood, but if more than 40% oxygen is necessary, other anaesthetic agents may be required to prevent awareness. If halothane is used, then direct myocardial depression may increase the difficulty in maintaining normotension (Prys-Roberts et al., 1972). There is little doubt that a patient who has been raised to the sitting position for a neurosurgical procedure has major changes in his cardiorespiratory status. By reducing the pre-load to the myocardium, a low cardiac index develops. If normotension is maintained, as was the case in all the patients studied, total peripheral resistance increases. The haemodynamic changes are similar to circulatory changes that occur in hypovolaemic but normotensive patients. Careful monitoring of both arterial and venous pressure is absolutely essential. Not only is arterial blood-gas analysis important, but useful information about the cardiac output can be obtained from the oxygen content of the mixed venous blood. Certainly it should not be assumed that a patient who has remained normotensive in the sitting position has an adequate circulatory status and anaesthetists should try to dissuade their neurosurgical colleagues from using the sitting position for neurosurgical procedures.

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EFFETS CARDIORESPIRATOIRES DE LA POSITION ASSISE POUR LA NEUROCHIRURGIE

RESUME

On a fait des recherches sur les effets cardiorespiratoires constatés sur les malades que l'on redresse de la position couchée pour passer à la position assise aux fins de neurochirurgie. Le changement provoque des diminutions marquées de l'indice cardiaque, du volume systolique de la Pa_{O_2} et du $\dot{Q}s/\dot{Q}t$ ainsi qu'une augmentation significative de la $(PA_{O_2}-Pa_{O_2})$ et de la résistance périphérique totale. On en a conclu que les malades qui maintiennent une normotension dans la position assise n'ont pas nécessairement un état circulatoire adéquat.

DIE KARDIO-RESPIRATORISCHEN AUSWIRKUNGEN DER SITZSTELLUNG BEI NEUROCHIRURGIE

ZUSAMMENFASSUNG

Untersucht wurden die kardio-respiratorischen Auswirkungen einer Veränderung neurochirurgischer Patienten von liegender in sitzende Stellung. Dies bewirkte Verringerung von Herzindex, Herzschlagvolumen, Pa_{O_2} und $\dot{Q}s/\dot{Q}t$, sowie einen wesentlichen Anstieg von $(PA_{O_2}-Pa_{O_2})$ sowie des gesamten peripheren Widerstandes. Daraus schliesst man, dass Patienten, die in der sitzenden Stellung Normotension bewahren, nicht unbedingt einen ausreichenden Kreislaufzustand besitzen.

EFECTOS CARDIORESPIRATORIOS DE LA POSICION SENTADA EN NEUROCIRUJIA

SUMARIO

Se averiguaron los efectos cardiorespiratorios del cambo de posición de pacientes sometidos a operaciones neuroquirúrgicas, desde una posición sentada a una de decúbito dorsal. El cambio ocasionó marcadas disminuciones del índice cárdiaco, de la descarga sistólica, del Pa_{O_2} y del Q_s/Q_t, junto con un aumento significativo del $(PA_{O_2}-Pa_{O_2})$ y de la resistencia periférica total. Se llega a la conclusión de que los pacientes que mantienen una normotensión en posición sentada no poseen necesariamente una condición circulatoria adecuada.

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PREMEDICATION IN CHILDREN UNDERGOING DAY-CARE SURGERY

P. D. BOOKER AND D. H. CHAPMAN

SUMMARY

An oral preparation of dichloralphenazone and paracetamol (Paedosed) was used as an alternative premedication to i.m. morphine and atropine in 562 children undergoing day-care surgery. From a series of observations made, both in hospital and at home, it appears that morphine has several disadvantages when compared with this mixture, provided that the latter is supplemented with i.v. analgesia for the more painful procedures.

There are differing views about the importance of premedication for children undergoing day-care surgery. Some argue that premedication is unnecessary (Steward, 1975), while others feel that heavy sedation is desirable (Shah et al., 1972). In an attempt to throw some light on this problem two contrasting premedication regimens were studied: morphine and atropine by i.m. injection *v.* an oral mixture of dichloralphenazone and paracetamol (Paedosed, Pharmax).

METHODS

Five hundred and sixty-two patients aged between 6 months and 10 years admitted for elective surgery as day-cases were randomly allocated to one of two groups. Group 1 (211 patients) was given morphine 250 μg kg^{-1} and atropine 20 μg kg^{-1} i.m. and group 2 (351) dichloralphenazone 40 mg kg^{-1}, paracetamol 20 mg kg^{-1} and atropine 15 μg kg^{-1}, by mouth. Group 2 was further subdivided: (a) 243 patients in whom pain after operation was considered unlikely and (b) 108 in whom it was likely. During induction of anaesthesia, patients in group 2b received either pentazocine 300 μg kg^{-1} or fentanyl 3 μg kg^{-1} i.v. The timing of premedication was variable (see Results).

The day ward is a separate ward within the main hospital with its own nursing staff. Parents are encouraged to stay with the children, although they do not accompany them to theatre. An anaesthetist and surgeon see each child and parent before the operation and before discharge, usually about 4 h after surgery.

Anaesthesia was induced with i.v. thiopentone 4 mg kg^{-1}, the trachea was intubated with uncuffed oral or nasal Magill tubes following either suxamethonium chloride 1.5 mg kg^{-1} or tubocurarine 800 μg kg^{-1} or pancuronium bromide 120 μg kg^{-1}, and the lungs were ventilated with 70% nitrous oxide in oxygen, the fresh gas flow calculated according to body weight (Nightingale and Lambert, 1978). Some patients received additional atropine 10–20 μg kg^{-1} during induction, if the anaesthetist so wished, for example when intermittent suxamethonium was used. After the use of a non-depolarizing relaxant, residual neuromuscular block was antagonized with a mixture of neostigmine 80 μg kg^{-1} and atropine 20 μg kg^{-1}.

Assessment. A questionnaire was provided for the anaesthetist, and a member of the day ward nursing staff as appropriate. The parents took home a simple questionnaire which they posted back on the following day. The patient's demeanour in the anaesthetic room was scored on a descriptive scale from 1 to 5, and the demeanour in the recovery room, assessed at 5-min after extubation, was scored similarly. The scores were simplified for analysis to *unacceptable* and *acceptable.* Oropharyngeal secretions at induction and antagonism of block were scored as *unnoticed, moderate* or *troublesome.* Difficulties in intubation and stridor or vomiting in the recovery room were noted. On return to the day ward, the patients were assessed regularly by the nursing staff with regard to pain, stridor, sore throat, vomiting and level of sedation. The pain stated was scored as *uncomplaining, discomfort only* or *severe* (requiring analgesia). If the nursing staff thought that analgesia was required after operation, Paedosed 0.4–1 ml kg^{-1} was given by mouth.

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From within the main series of 562 patients, a number of subgroups were examined, matched for age and type of operation. One hundred from group 1 (morphine) were compared with 100 patients from group 2a (Paedosed+atropine only). These are referred to as groups 3 and 4. Three matched groups of 54 patients each, who had "painful" operations, were examined: group M = morphine; group P = Paedosed premedication and pentazocine supplement; group F = Paedosed premedication and fentanyl supplement.

Statistical analysis. Student's *t* test was used to evaluate the difference between groups 1 and 2 and between groups 3 and 4. The difference between groups M, P and F was analysed using the Chi-square test. A probability value of less than 0.05 was considered statistically significant.

RESULTS

Eighty-five per cent of parents returned the questionnaires.

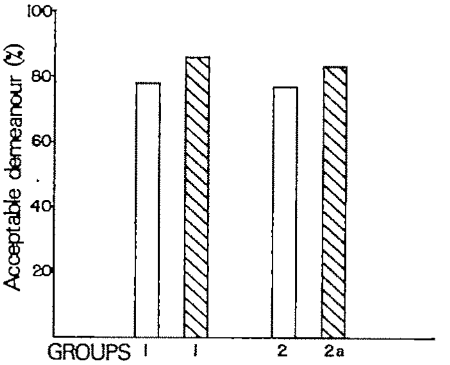

FIG. 1. Demeanour before □ and after ■ operation in groups 1 and 2.

Demeanour. There was no significant difference ($P > 0.05$) in the proportion of patients with an acceptable demeanour before and after operation in groups 1 and 2 (fig. 1). Of those with an unacceptable demeanour in the anaesthetic room, 25% in group 1 and 38% in group 2 had received premedication less than 40 min before induction. Only 10% of patients with an acceptable demeanour in either group had received premedication so late.

In groups 3 (morphine) and 4 (Paedosed) the proportions of children with acceptable demeanour after operation were 89% and 80%. In the smaller matched groups M, P and F, the percentages were 81, 85 and 94 (fig. 2). In all groups, approximately 30% of the patients who had unacceptable demeanour in the recovery room also had an unacceptable demeanour in the anaesthetic room.

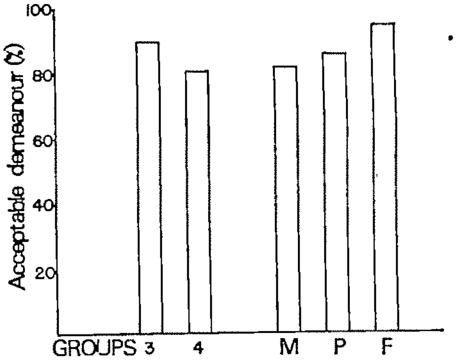

FIG. 2. Demeanour after operation in the matched groups.

Secretions. Three per cent of patients in group 2 (Paedosed+oral atropine) had troublesome secretions at induction. There were no cases in group 1 (i.m. atropine). Of those patients in the Paedosed subgroups (2a, P and F) who were given additional parenteral atropine at induction only 3% had troublesome secretions at the time of antagonizing the myoneural block. However, when additional atropine was not given, this figure increased to 17%. Excessive secretions at antagonism were seen in only 1% of patients in group 1. Ten (90%) of those in group 2 with troublesome secretions at induction had been given premedication less than 50 min before induction. A relationship with time of administration was not evident in patients with troublesome secretions at antagonism, nor in patients who received i.m. atropine.

Intubation difficulties. In 13% of the series as a whole more than one attempt at intubation was necessary, mainly because the size of the tracheal tube required differed from that predicted (Browne, 1969). There were no other intubation difficulties in any children.

Stridor and sore throat. Twelve per cent of patients complained of sore throat while in hospital, but only 2% did so at home. Eleven per cent complained of hoarseness or had mild stridor in hospital, but only one patient complained of this at home. No patient had to be detained in hospital because of stridor.

Pain after operation, in hospital and at home (*fig.* 3). There was no significant difference between groups 3 and 4 in the proportion of children complaining of pain while in hospital (12% and 8% respectively); no child in either group required analgesia after

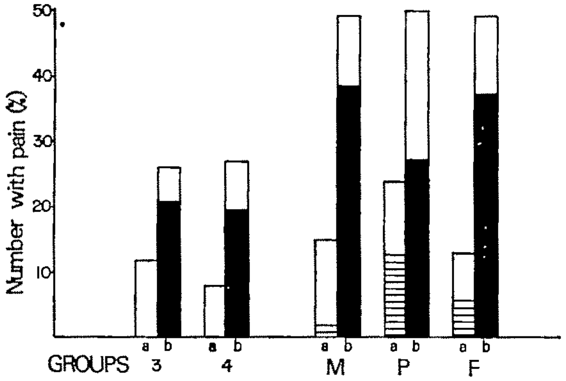

FIG. 3. Pain after operation in the matched groups. a = in hospital; b = at home; ■ = pain for the first time; ▤ = postoperative analgesia required.

operation. Twenty-seven per cent of both groups complained of pain at home, 80% of these complaining of pain for the first time. Fifteen per cent (seven patients) in group M and 13% (six) in group F complained of pain in hospital, although only one child in the morphine group (M), as opposed to three children in the fentanyl group (F), required analgesia after operation. Twenty-four per cent of patients (12) in group P complained of pain in hospital and of these, seven required an analgesic. The differences between the groups were not statistically significant. Approximately 50% (26) of patients in all three groups complained of pain at home, of whom the majority (approximately 20 in each group) were complaining for the first time.

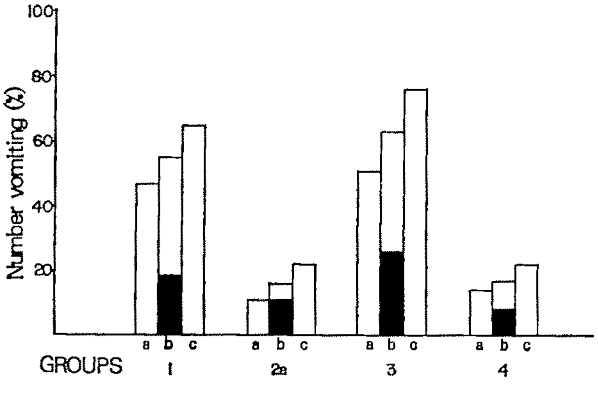

FIG. 4. Postoperative vomiting in groups 1, 2a, 3 and 4. a = in hospital; b = at home; c = total vomiting. ■ = vomiting for the first time.

Sedation after operation. Eleven per cent of patients in group 1 and 3% in group 2a were still drowsy 4 h after extubation. The figures in groups 3 and 4 were 10% and 2% respectively.

Vomiting in hospital and at home. Forty-seven per cent of patients in group 1 and 11% in group 2a vomited while in hospital (fig. 4) ($P < 0.01$). This difference was evident at home also (group 1, 55%; group 2a, 16%). Overall, 65% in the morphine group vomited at some time, but only 22% in the Paedosed group. In the matched groups 3 and 4 this difference was even more obvious.

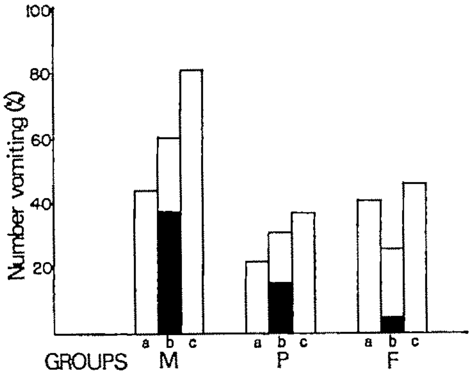

FIG. 5. Vomiting in groups M, P and F. a = in hospital; b = at home; c = total vomiting; ■ = vomiting for the first time.

In groups M, P and F (fig. 5), there was still a difference between morphine and the other two groups. In group F, 50% of those vomiting in hospital did so only in the recovery room, whereas of the 6% of groups M and P who vomited in the recovery room, the majority also vomited in the day ward.

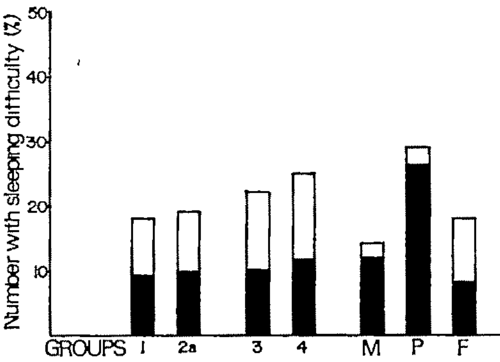

FIG. 6. Sleeping difficulty in all groups. ■ = those also complaining of pain.

Sleep at home (fig. 6). In groups 1 and 2a, 82% of patients were able to sleep quickly, but of those children unable to sleep, 54% were also complaining of pain. In groups 3 and 4, 78% and 75% went off to sleep quickly. Of those who found difficulty in sleeping, 45% in both groups were in pain. In the smaller matched groups, the highest percentage of patients sleeping quickly was in the morphine group (M), but of those with difficulty in sleeping, 85% in groups M and P also complained of pain; 44% in group F.

Anorexia. Twenty-six per cent of patients in group 1 and 13% in group 2a were anorexic on the following day. These proportions were similar in groups 3 and 4. Twenty per cent of the morphine group (M), 29% of the pentazocine group (P) and 12% of the fentanyl group (F) were anorexic on the next day.

DISCUSSION

The combination of moderately heavy premedication (oral trimeprazine and i.m. morphine), i.v. induction, muscle relaxation and controlled ventilation with nitrous oxide and oxygen is one which has proved itself over the years to be safe and trouble-free (Rees, 1959). However, many children, especially those admitted for repeated minor procedures, remark that their i.m. injection before operation is the worst thing that happens to them in hospital (Doughty, 1959; Boyd and Manford, 1973). An ideal premedication would have analgesic and sedative properties, without emetic or other serious side-effects. Paedosed appeared to offer most of these qualities, and atropine was added as an antisialagogue.

It is often presumed that premedication has a major influence on the patient's demeanour in the anaesthetic room. However, in this study, it would appear that the premedication itself was of only minor importance. Other factors, such as the patient's personality, the attitude of the ward staff and parents, and previous hospital experience, may be of greater importance.

In group 1, a very dry oropharynx was common, which is undesirable and unpleasant for many patients. The amount of atropine added to the Paedosed was 15 $\mu g\ kg^{-1}$. However, up to 17% of patients who had been given this mixture had troublesome secretion on antagonism of myoneural blockade; this high figure was reduced substantially by giving additional atropine at induction, but rather than advising this as a routine, it was decided that the oral dose should subsequently be increased to 20 $\mu g\ kg^{-1}$. This avoids complicating the technique and possibly increasing the frequency of side-effects (Riding, 1975).

The significant difference ($P < 0.01$) between the morphine and Paedosed groups with regard to drowsiness after operation is worth emphasizing; it is neither necessary nor desirable for any child undergoing a pain-free procedure to remain sedated for hours after the operation has finished.

Pain in children is notoriously difficult to evaluate and was assessed by parents and the nursing staff. Perhaps surprisingly, Paedosed proved to be very effective in all 15 patients requiring analgesia after operation. The number of patients complaining of pain while at home is rather disturbing. Our figures may contain a proportion of those seeking attention or with only very minor discomfort. Nonetheless, it would seem advisable to issue to the parents an analgesic for use at home, with appropriate instructions. The successful use of Paedosed in the period after operation within the hospital suggests that only a relatively mild analgesic may be required.

A high proportion of children in group P (pentazocine) complained of pain while in hospital, more required analgesia after operation, and more had difficulty in sleeping, than in any other group. This may reflect the low dose of pentazocine administered.

In this study morphine had a pronounced emetic effect which lasted into the period following surgery, with many patients vomiting for the first time at home. This long duration of action contrasted with that of fentanyl, where the peak emetic effect was within the first hour of administration. The small percentage of children vomiting after Paedosed was increased following supplementation by fentanyl or pentazocine, but did not reach the much higher value produced by morphine. It is worth emphasizing that repeated vomiting is not only an unpleasant experience, but may also be a major factor in the fluid balance of an already dehydrated child (Holden and Maker, 1965).

The proportion of children complaining of sore throat after operation compares favourably with other series (Ahlgren, Bennett and Stephen, 1971; Steward, 1975). Incomplete antagonism of blockade may explain some of those cases with temporary stridor after operation, but the number of children (11%) with hoarseness in hospital is greater than that quoted in other series (Shah et al., 1972). All but one patient had recovered the normal voice at the time of discharge from hospital. There was no obvious relationship between complaints of mild hoarseness and repeated attempts at tracheal intubation.

It is reassuring to note that a narcotic analgesic (fentanyl) can be administered to children without necessarily increasing the frequency of anorexia after operation. The figures for the Paedosed and fentanyl groups compare well with those quoted in other series (Ahlgren, Bennett and Stephen, 1971; Steward, 1973).

We conclude that parenteral morphine premedication is far from ideal for children undergoing minor surgery as day patients, and the combination of a mild sedative oral premedication with i.v. analgesic supplementation merits further study.

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PREMEDICATION ADMINISTREE A DES ENFANTS SUBISSANT UNE INTERVENTION CHIRURGICALE SANS SEJOUR HOSPITALIER

RESUME

On a utilisé une préparation orale de dichloralphénazone et de paracétamol (Paedosed) comme prémédication de rechange à l'injection intramusculaire de morphine et d'atropine, sur 562 enfants subissant une intervention chirurgicale sans séjour hospitalier. D'après les observations qui ont été faites, aussi bien à l'hôpital qu'à la maison, il semblerait que la morphine présente plusieurs inconvénients par rapport à ce mélange, mais à la condition toutefois que ce dernier soit renforcé d'une injection analgésique intraveineuse pour les interventions les plus douloureuses.

VORBEHANDLUNG VON KINDERN FÜR AMBULANTE EINGRIFFE

ZUSAMMENFASSUNG

Ein oral gegebenes Präparat aus Dichloralphenazon und Paracetamol (Paedosed) wurde als alternative Vorbehandlung zu intravenös verabreichtem Morphium und Atropin wurde bei 562 Kindern für ambulante Eingriffe verwendet. Bei Reihenbeobachtungen im Krankenhaus und zu Hause ergab sich, dass Morphium im Vergleich mit dieser Mischung einige Nachteile hat, wenn diese Mischung bei schmerzhafteren Eingriffen durch intravenös verabreichte Schermzstillmittel erganzt wird.

PREMEDICACION EN NINOS SOMETIDOS A CIRUJIA AMBULATORIA

SUMARIO

Se usó una preparación oral de dicloralfenazona y paracetamol (Paedosed) como premedicación alternativa en vez de morfina y atropina i.m. en 562 niños sometidos a cirujía ambulatoria. A raíz de una serie de observaciones realizadas tanto en el hospital como en la casa, parece que la morfina tiene varias desventajas cuando se la compara con esta mezcla, siempre y cuando a esta última se la acompaña por una analgesia i.v. para las intervenciones más dolorosas.

Br. J. Anaesth. (1979), **51**, 1089

REGURGITATION DURING PELVIC LAPAROSCOPY

B. L. Duffy

SUMMARY

In two of 93 fasting patients undergoing gynaecological laparoscopic procedures, there was evidence of gastric regurgitation to the pharynx. It is suggested that prophylactic measures should be taken in such patients to avoid the acid aspiration syndrome.

Although all surgical patients should be considered to be at risk from the aspiration of gastric contents (Hester and Heath, 1977) it is important to identify high-risk groups. During pelvic laparoscopy there are several factors which increase intra-abdominal pressure and may cause regurgitation, including the lithotomy position, steep head-down tilt, insufflation of gas to the peritoneal cavity and pressure on the abdomen by the surgeon.

The frequency of regurgitation in patients undergoing laparoscopy was assessed in a group of female patients.

PATIENTS AND METHODS

Ninety-three young females undergoing gynaecological operations through the laparoscope were studied. All were in good general health, apart from one suffering from asthma and receiving steroids, and one with diabetes receiving insulin. The ages range was 17–44 yr; weight range 44.5–100 kg.

They were admitted to hospital as day-stay patients on the morning of the operation, and each was given lorazepam 2.5 mg orally immediately following admission. An exception was the diabetic patient, who was not given premedication.

The patients were questioned about previous general medical history, and specifically about a history of peptic ulceration, indigestion or heartburn.

A standard method of anaesthesia was used. Preoxygenation was followed by i.v. atropine 0.6 mg, fentanyl 50 μg and droperidol 2.5 mg, thiopentone 200–350 mg and alcuronium 10–15 mg. The trachea was intubated with a 7.5-mm cuffed tube, and the cuff inflated. Manual ventilation with a face-mask was not attempted. The lungs were ventilated artificially with halothane (intermittent) in 33% oxygen in nitrous oxide, using a Manley ventilator.

The gynaecologist placed the patient in the lithotomy position with steep head-down tilt. The insufflating gas was nitrous oxide (carbon dioxide if diathermy was used). At the end of the procedure laryngoscopy was performed before antagonism of alcuronium. Test paper (Merck's Special Indicator) was applied to any fluid present in the pharynx. When possible, the pool was aspirated with a syringe for subsequent analysis with a pH electrode (BMS 3 MK 2, Radiometer, Copenhagen).

RESULTS

Ninety-one patients had no gross pooling in the pharynx, and pH on the test strip was greater than 5.0 in all cases. Two patients had regurgitated. The 10th patient in the series had a pool of 12 ml with pH 3 unit. In the laboratory the pH was found to be 2.30. This patient weighed only 44.5 kg, and had no history of peptic ulceration or indigestion. The 93rd patient had a bile-stained pool of approximately 3 ml with pH greater than 7, the upper limit of the test paper used. The actual pH was 8.05. This patient weighed 80 kg, but had no gastrointestinal symptoms.

In view of the positive findings in this small series, the study was terminated and prophylactic measures instituted for subsequent patients.

DISCUSSION

It has been shown that fasting patients presenting for pelvic laparoscopy may have gastric contents of sufficient volume and acidity to produce Mendelson's syndrome if aspiration should occur (Tay and Chiu, 1978). The present study, which was commenced before the publication of that previous paper, shows that regurgitation may occur during laparoscopy.

Although the Trendelenburg position should prevent regurgitated fluid from entering the airway, this is not used universally. Also, some anaesthetists

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do not routinely intubate the trachea. Local and regional analgesia do not necessarily guarantee complete safety, since the associated use of heavy sedation may obtund the laryngeal reflexes.

Apart from mechanical causes of regurgitation, there are pharmacological factors. The tone of the lower oesophageal sphincter (LOS) is decreased by both atropine and hyoscine (Brock-Utne, Rubin et al., 1977) and it is possible to demonstrate stress reflux in patients who have received these drugs. Since metoclopramide markedly increases LOS tone (Brock-Utne et al., 1976) it would seem advisable to use this drug routinely. Metoclopramide and atropine have opposing effects and atropine should be avoided. There are specific indications for its use.

Prolonged fasting does not guarantee an empty stomach (Brock-Utne, Moshal et al., 1977; Tay and Chiu, 1978).

The present results confirm that patients undergoing pelvic laparoscopy are at risk of developing the acid aspiration syndrome. In addition to the recommendations for the conduct of general anaesthesia for laparoscopy (Chiu and Ng, 1977), I would suggest that magnesium trisilicate should be administered before operation to all patients undergoing the procedure, whether under local, regional or general anaesthesia. When general anaesthesia is administered, intubation of the trachea is essential. Consideration should be given to using metoclopramide before induction, and perhaps avoiding atropine unless specifically indicated.

ACKNOWLEDGEMENTS

I wish to thank the Salisbury gynaecologists whose patients were studied, Dr G. P. T. Barclay and Dr M. M. Friedman for laboratory assistance, and Mrs F. Fraser for typing the manuscript.

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REGURGITATION PENDANT UNE LAPAROSCOPIE PELVIENNE

RESUME

On a constaté sur deux patientes à jeun (sur un total de 93) subissant une intervention gynécologique de laparoscopie, l'évidence d'une régurgitation gastrique au niveau du pharynx. On suggère dans cet article de prendre des mesures prophylactiques vis-à-vis de ces patientes afin d'éviter le syndrome de l'aspiration acide.

RÜCKSTAU WÄHREND LAPAROSKOPIE IM BECKEN

ZUSAMMENFASSUNG

Bei zwei von 93 fastenden Patienten kam es während laparoskopischer gynäkologischer Vorgänge zu gastrischem Rückstau zum Schlund. Es wird empfohlen, Vorbeugungsmassnahmen bei solchen Patienten zu treffen, um ein Saureeinatmungssyndrom zu vermeiden.

REGURGITACION DURANTE LAPAROSCOPIA PELVICA

SUMARIO

En dos de las 93 pacientes en ayunas sometidas a intervenciones ginecológicas laparoscópicas, hubo pruebas de regurgitación gástrica en la faringe. Se sugiere tomar medidas profilácticas en dichas pacientes para evitar el síndrome de aspiración ácida.

CORRESPONDENCE

HARRINGTON ROD SPINAL FUSION

Sir,—The use of distraction and compression rods in the treatment of scoliosis was originally described by Harrington (1962). One of the complications of this operation is paraplegia, with a reported frequency of 0.1% (Harrington, 1971). To prevent this complication, patients are wakened during operation to check the voluntary motor power of the limbs. A variety of wake-up techniques has been described (Vauzelle, Stagnara and Jouvinroux, 1973; Crawford et al., 1976; Sudhir et al., 1976). The success of extradural bupivacaine in reducing blood loss during intervertebral disc operations, and the associated sensory blockade prompted us to incorporate extradural analgesia into the wake-up technique during Harrington Rod procedures.

Five consecutive patients aged between 18 and 26 yr were studied. All had idiopathic scoliosis and were otherwise healthy. Before operation, they were informed of the wake-up procedure and received papaveretum 10 mg and hyoscine 0.2 mg i.m.

Anaesthesia was induced with thiopentone 5 mg kg^{-1} and tracheal intubation facilitated by suxamethonium 1.5 mg kg^{-1}; with the patient in the lateral position and with a 10° Trendelenburg tilt, 0.25% bupivacaine 20 ml with adrenaline 1 : 200 000 was injected extradurally via L3–4 interspace. After 3 min, the patient's position was altered to 10° head up tilt, and a further 20 ml of solution was injected. Finally, the patient was placed prone on the operating table; anaesthesia was maintained with 60% nitrous oxide in oxygen and muscle relaxation achieved with tubocurarine 30 mg.

During operation arterial pressure varied from 70 to 90 mm Hg but was stable for each patient. Blood loss varied from 525 to 1250 ml and was replaced with stored blood.

When the Harrington Rods had been inserted and full distraction accomplished, the wakening process was instituted; neuromuscular blockade was antagonized with the total calculated dose of atropine and neostigmine. In all patients, spontaneous ventilation and a response to verbal commands was achieved within 2 min. As soon as movement of the hands and feet was noted, patients were re-anaesthetized with thiopentone 500 mg and the lungs were ventilated with 60% nitrous oxide in oxygen. I.v. analgesics and myoneural blocking drugs were not required. At the end of the operation, all five patients breathed spontaneously within 3 min, although two required persistent verbal commands. None had any recollection of the procedure.

We found that this technique simplified the intraoperative wake-up procedure; i.v. analgesic agents, analgesic antagonists and tranquillizers were avoided, as indeed was further myoneural blockade. The technique provided good analgesia after operation. Bupivacaine 0.25% achieved sensory blockade, but preserved the motor function necessary for the functional monitoring of spinal cord activity.

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HAEMOPTYSIS AFTER PULMONARY ARTERY CATHETERIZATION

Sir,—In their paper describing haemoptysis after pulmonary artery catheterization, Krantz and Viljoen (1979) report pulmonary artery pressures of 40/15 mm Hg, with a "wedge" of 18 mm Hg in their patient. I submit that this is at once a physiological impossibility and the cause of the complication. It is not possible to have a pulmonary capillary wedge pressure greater than the diastolic pulmonary artery pressure; to do so would have the circulation reverse itself at the end of each cardiac contraction! It is possible that the tip of the catheter was occluded by over-zealous advancement during the initial passage and this caused the perforation of the small pulmonary vessel. Migration of the catheter after removal of the introducer was not of importance. It should be remembered that the catheter must not be advanced further after a typical wedge tracing is identified, lest this complication occur.

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REFERENCE

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Sir,—We agree that a pulmonary capillary "wedge" pressure greater than the pulmonary artery diastolic pressure is an unusual finding and difficult to explain on a physiological basis. There are, however, three circumstances in which such readings may be obtained, all of which may have occurred in our patient.

First, in the presence of mitral incompetence the V-wave is transmitted so that an electronically obtained "wedge" pressure will be greater than the pulmonary artery diastolic pressure. This finding is well-documented (Swan and Ganz, 1975).

Second, the figures we quoted in our report were not recorded simultaneously, but were separated by a 3–5 min interval. It is possible that the mere passage of the catheter reflexly elicited an increase in wedge pressure.

Third, inflation of the balloon may distort the position of the distal orifice so that an electronic artefact is obtained.

We further agree that perforation of a small pulmonary artery was possible, but would like to re-emphasize that the blood was bright red. This suggests that the bleeding was not from the pulmonary artery. Furthermore, in a patient with pulmonary hypertension, perforation of a pulmonary artery would have caused more catastrophic haemorrhage than the measured 200 ml.

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SKIN SENSITIVITY TO HALOTHANE VAPOUR

Sir,—The following anecdote is recounted as I do not remember having seen such a phenomenon reported before.

Recently a new nurse joined our operating room team. One day at the conclusion of the list she noticed that her face and neck had become red with itching; this increased and oedema of the eyelids developed. The discomfort was such that she could not sleep that night. On the following morning she still had residual flush of her face and puffy eyelids, which did not subside for 2 days. She then remembered that this had occurred to a milder extent one day in previous week.

On reflection, we remembered that on each occasion she had assisted at the induction of anaesthesia in an infant when I had used halothane and oxygen, using a face-mask fitted with a spill valve on the connector. I sat at the head of the table and the nurse stood on the right side facing me and holding the infant by the arms so that she was leaning forward directly over the expiratory valve: she thus received the spill of 3 litre of oxygen with up to 2% halothane directly in the face. The "paediatric set" is the only anaesthetic apparatus we use which has no scavenging device. All our anaesthetic machines are fitted with closed circuits and the gases from the spill valves are effectively removed from the room.

Scientific principles would require that I should ask the young lady to submit to an experimental exposure to halothane vapour and deliberately reproduce the effect. I am loath to do this as it is clearly an unpleasant experience, unless someone can adduce further evidence to confirm or deny that this is in fact a case of sensitivity to halothane vapour.

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EXTRADURAL ANALGESIA FOR CAESAREAN SECTION

Sir,—In his lucid editorial under the above title, Dr Donald Moir (1979) has summarized the current status of the technique. Appreciation of the physiological and pharmacological principles to which he refers should enable an anaesthetist in ideal circumstances, and after full unbiased discussion with the mother, to offer central neural blockade (CNB) by either extradural (EDB) or subarachnoid (SB) routes as an alternative to general anaesthesia.

In addition to the advantages which Dr Moir has outlined, there are other potential, yet poorly documented, merits of CNB (Brownridge, 1979a, b). First, paternal participation at the birth is possible; a preliminary survey has shown considerable demand for the satisfaction of this shared experience. Second, an earlier return of appetite and oral intake is possible using EDB rather than opiates for analgesia. This is supported by Nimmo and colleagues (1978) who described improved gastric emptying following hysterectomy with extradural analgesia and by Gelman and colleagues (1977) who used electroenterographic studies in patients undergoing cholecystectomy with or without EDB. Third, successful lactation and breast feeding is more likely to become established following early mother–infant contact (Salariya, Easton and Carter, 1978). Fourth, although recent authors, cited by Dr Moir, have shown a similar infant outcome after EDB and general anaesthesia, Hodgkinson and colleagues (1978) have demonstrated superior neonatal behavioural scores following Caesarean section with SB. Fifth, blood loss is reduced, as is the need for transfusion. Finally, EDB may reduce the frequency of deep vein thrombosis after surgery by virtue of large increases in lower limb flow (Cousins and Wright, 1971) and by inhibiting platelet aggregation. These factors may override any possible disadvantage from diminished leg movements.

Undoubtedly, intra-abdominal surgery is a major test of CNB, but maternal desire to be aware of birth is developed so strongly in some women that unpleasant symptoms are accepted. Analyses of the degree of discomfort and side-effects are difficult and it is not surprising that there is considerable variation in their reported frequency. Nevertheless, the important factor is the overall recollection of the experience. Despite commonly recollected discomforts, most women are enthusiastic about the technique (Brownridge, 1979b).

Further refinements in technique and drug application may provide improvements. Dr Moir refers to imperfect and unpredictable sacral nerve blockade as a common source of discomfort following EDB. Although patient positioning is advocated by many authorities as a useful manoeuvre to improve spread, I am sceptical about its value. A simultaneous caudal block may be used to ensure sacral nerve root blockade, but systemic toxicity is more likely. The influence of local analgesic agents on the fetus remains controversial, but it seems sensible to reduce circulating concentrations to a minimum.

An alternative approach is to combine extradural blockade with subarachnoid block for Caesarean section (Brownridge, 1979a). Insertion of an extradural catheter in an upper lumbar interspace is followed by subarachnoid block and bilateral somatic blockade achieved by positioning of the patient. In this way, a rapid profound block of all sacral nerve roots is obtained. This combined blockade allows greater flexibility, a reduced total dose of local analgesic agent and permits continuous EDB for analgesia after operation. Initial experience with this technique has been encouraging. The frequency of spinal cephalgia is small.

Despite the use of oxytocin in preference to ergometrine, I have found the frequency of nausea to be greater with this drug than is commonly reported. However, it is usually transient and occurs before surgery; is it possible that magnesium trisilicate may be responsible for this?

Although the measures outlined to prevent hypotension are adequate in most instances, I am surprised that Dr Moir did not mention the prophylactic administration of atropine and the value of a vasopressor. Ephedrine should be immediately available since this agent is rapidly effective in reversing the undesirable effects of hypotension, but does not decrease uterine blood flow (Ralston and Schnider, 1978). Supplementary oxygen is surely desirable, especially before delivery.

The concluding sentences of Dr Moir's editorial are particularly pertinent. Trainees must receive supervision and support and no anaesthetist should be expected to embark upon such a potentially hazardous procedure without the competence and confidence to manage the patient's physical and psychological needs.

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Sir,—I thank Dr Brownridge for his complimentary remarks. The aims of my editorial were to present a short, balanced account of the major advantages and disadvantages of extradural analgesia for Caesarean section and to draw attention to a technique which can ensure adequate analgesia in the great majority of patients. It was not intended to present a fully detailed review. Dr Brownridge shares my cautious enthusiasm for the method and our ideas differ only on quite minor details.

Five additional advantages are listed for extradural analgesia. I agree that maternal and paternal participation at the birth are usually desirable, although there is sometimes resistance by obstetricians to the presence of the father. If the father is to be present he should join the mother only when the block is complete and any episodes of hypotension, nausea or vomiting have been treated. The condition of the mother after operation is impressively good. Not only can she eat and drink at an early stage, but she is alert, pain-free and able to breast feed. The reduction in blood loss to which Dr Brownridge refers is substantial and was demonstrated in an earlier publication (Moir, 1970).

Our experiences with a technique of extradural analgesia which ensures sacral nerve block will be reported in detail elsewhere (Thorburn and Moir, 1979). Analgesia was adequate for surgery in 98% of mothers and sacral block is achieved by injecting in the sitting position. Alternative methods of achieving sacral analgesia include the two-catheter technique, an additional caudal block or an additional subarachnoid block as suggested by Dr Brownridge. As Dr Brownridge rightly points out it is the recollection of the overall experience which matters and in our series less than 2% of mothers stated that they would not choose extradural analgesia for a subsequent Caesarean section.

The effects upon the fetus and neonate have been described recently by several authors. Fetal acidosis has been reported as similar to or slightly greater than that associated with general anaesthesia (Wallis et al., 1976; James et al., 1977; Palahniuk et al., 1977; Hollmén et al., 1978; Downing, Houlton and Barclay, 1979). Our own observations suggest that if aorto–caval occlusion is avoided and hydration before and during operation is maintained then fetal acidosis is of similar extent after extradural and general anaesthesia. An important observation is that fetal oxygen consumption is not decreased by extradural block and placental blood flow is not significantly reduced in the absence of arterial hypotension (Jouppila et al., 1978; Hollmén et al., 1978).

Whereas general anaesthesia consistently depresses neurobehavioural responses in the neonate for up to 48 h, these effects are absent after Caesarean section under extradural block with lignocaine, bupivacaine and etidocaine in the absence of arterial hypotension (Lund et al., 1977; Palahniuk et al., 1977; Hollmén et al., 1978; McGuiness et al., 1978). Respiration is rapidly established at birth. The technique advocated involves the use of a mean dose of 115 mg of bupivacaine (range 60–170 mg). McGuiness and others (1978) used a mean dose of 168 mg of bupivacaine and there were no signs of neurobehavioural impairment in the neonates and toxic blood concentrations did not occur.

I agree that ephedrine should be immediately available and we use this agent if arterial hypotension does not respond rapidly to postural change and i.v. fluids. In our experience also, nausea or vomiting are quite frequent (17% in our series) and not always related to hypotension and certainly not to ergometrine, which is not used. All patients inhale a mixture of 20% nitrous oxide in oxygen until delivery, thereby benefiting from a high $F_{I_{O_2}}$ and a degree of inhalation analgesia.

Extradural analgesia can be a safe and effective technique for Caesarean section in skilled and careful hands. The delivery of the infant into the arms of a conscious and pain-free mother is one of the most exciting and rewarding moments in medicine.

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HUMIDIFICATION IN ANAESTHESIA

Sir,—I have read with interest the editorial written by Dr Bernard Hayes (1979). While British insularity may have protected the country in the past it should no longer involve medicine which is now a well publicized science at the international level. It is high time that British authors document themselves by extensively reading foreign journals. In the last decade there have been well over 250 publications on the humidification of anaesthetic and intensive care equipment. This includes publications in English from America, Australia, Canada and Britain, and French and Hebrew articles. I am omitting the German and Italian literature, which I have only superficially consulted, but I have seen several excellent translations of outstanding Japanese work. While I have been impressed by the style and the way Dr Hayes presented his material, I have found it too one-sided and it ignores the information available in the foreign literature. In addition, the last line of his editorial has long been answered on many occasions. My advice to British anaesthetists is to read foreign publications in addition to their own. Wake up Britain!! The time is ripe for you to regain the high position you held in the days of Addison, Hodgkins and Hughlings Jackson. Insularity is a thing of the past and is synonymous today with provincialism. Let's get rid of it and read the discoveries made both outside and inside the British Isles.

JACK CHALON
New York, U.S.A.

REFERENCE

Hayes, B. (1979). Humidification in anaesthesia. *Br. J. Anaesth.*, **51**, 389.

"EXPLOSION" DURING SPINAL ANAESTHESIA

Sir,—Sudden, unanticipated events in the operating theatre can be quite unnerving. Recently, administration of a seemingly routine spinal anaesthetic was brought to an abrupt halt at the moment of dural puncture by a violent report which echoed through the operating room. Rapid investigation found the patient unaffected and unharmed, nor was anyone else in the room injured. The source of the noise, which seemed to come from the front of the laterally recumbent patient, proved to be the now-ruptured bladder of the arterial pressure cuff. The bladder was replaced, the spinal anaesthetic administered, and the remainder of the case proceeded uneventfully.

The anaesthesia machine in the room was equipped with an automatic arterial pressure cuff inflator, and an observer had inadvertently leaned against the "inflate" button with the bleed valve closed. Attempts were made later to duplicate this event, and were unsuccessful until the bladder was made to protrude 1 cm from the cuff. Figure 1 illustrates the situation just before rupture of the bladder.

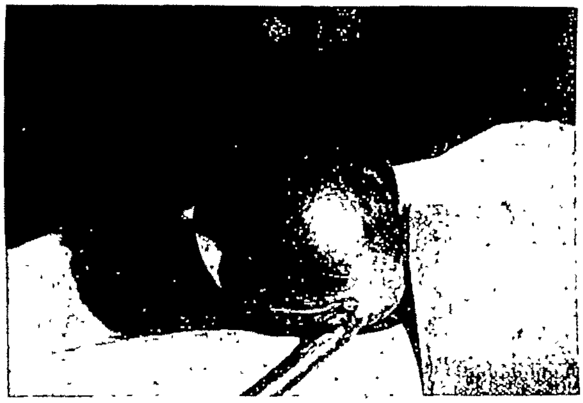

FIG. 1. The bladder just before rupture.

Thus, a rather startling "explosion" in the course of a spinal anaesthesia was of relatively little consequence once its cause was understood. It is hoped this report will lead to prevention or quicker appreciation of similar events in operating suites elsewhere and thereby attenuate what in our case was a quite marked increase in anxiety.

JOSEPH A. STIRT
ROBERT D. KAUFMAN
Los Angeles, U.S.A.

Br. J. Anaesth. (1979), **51**, 1095

BOOK REVIEWS

Nitroprusside and Other Short Acting Hypotensive Agents. International Anesthesiology Clinics, **16** (2). Edited by A. D. Ivankovitch. Published by Little Brown & Company, Boston. Price: Series subscription $35 per year.

This edition of *International Anesthesiology Clinics* is devoted to the subject of drugs that are most useful for the short-term control of arterial pressure, both for the management of hypertensive emergencies and for the induction of hypotension during anaesthesia. The book has no less than 18 authors, all Americans, and covers most of the drugs in common use at the present time. Much emphasis is placed on the detailed pharmacology of the drugs and much less, in general, on techniques and indication for their use.

The first few chapters, comprising nearly half the book, are devoted to sodium nitroprusside (SNP) and provide the most detailed account of the drug so far published. There are, however, errors of detail in the first chapter on metabolism of SNP—solutions are stable for much longer than 4 h if protected from the light; the normal concentrations quoted for plasma thiocyanate are much too great for non-smokers; the half-life of SNP is much less than 2 h. The exact role of the rhodanase system is poorly explained. Otherwise these chapters contain an interesting, detailed and accurate account of the properties, cardiovascular effects and therapeutic uses and modes of administration of the drug, although the 12 pages devoted to an experimental computerized system for the automatic administration of SNP could be regarded as excessive. The remaining six chapters are devoted to the ganglion blocking drugs, diazoxide, α-adrenergic blockers and hydrallazine. They include an excellent version of the therapeutic potential of glyceryl trinitrate by John Stetson although, at the time of writing, the drug had not yet received FDA approval.

The misuse of short-acting hypotensive drugs by clinicians who have failed to understand their exact physiological effects and mode of action is not uncommon, and for this reason the book should be read by all who use them. So much relevant information on the subject in a single volume is not easily obtainable elsewhere.

P. V. Cole

Lecture Notes on Anaesthetics. By John N. Lunn. Published (1979) by Blackwell Scientific Publications. Pp. 170; illustrated; indexed. Price £4.

What should medical students learn about anaesthesia? Dr Lunn suggests that they need to know the role of anaesthesia and anaesthetists in modern medical practice, to understand how to look after unconscious patients, to acquire skills necessary for resuscitation and to appreciate the problems of intercurrent disease in patients needing an anaesthetic. His book provides a guide to achieving these aims and succeeds, except perhaps in the first. On reading all the book the student will get some insight, but surely books of this type could start by explaining why anaesthesia and anaesthetists are needed at all. Apart from this, the book is worth recommending to medical students and house surgeons.

John Norman

Current Topics in Anaesthesia Series. 1. *Intravenous Anaesthetic Agents*. By John W. Dundee. Published (1979) by Edward Arnold Ltd. Price £9.25.

The first question that any reviewer is bound to ask is what place there can be for yet another book on i.v. anaesthetic agents, particularly one which, by virtue of its authorship, must reflect a familiar point of view. Even more is one tempted to ask what place there can be for a whole *series* of new books on current topics, of which this is the first. Pragmatically, the justification must be that there is a demand: as long as books can be sold, at a profit to the publisher, authors will be invited to produce them. Why, then, the demand? I well remember a distinguished colleague, some years ago, calculating that if a doctor subscribed to all the journals he ought to read he would need to employ two secretaries to remove the wrappers. Indeed, the literature is now so extensive, so international and so diversified in its content that more and more people, at various stages of their careers, are inclined to welcome relatively simple texts which summarize recent knowledge in a particular field. If there is a place for such books, then, it is important that they be exceedingly well prepared.

This book was admittedly written in a hurry. The author has drawn on a variety of sources of material, indicated by the fact that one chapter, on etomidate, is more comprehensive than others and has the references in a different style. Colleagues of the author were also asked to contribute at various points; there is a good chapter by Clarke on hypersensitivity reactions but the chapter on "Some Clinical Aspects" is rather scrappy and it would have been preferable for much of the material to be incorporated in the relevant chapters on individual groups of drugs. There is a chapter on "Balanced Techniques", rather than neuroleptanaesthesia, which seems to be something of a debunking exercise, and the chapter on total i.v. anaesthesia is thin, containing only two references later than 1953. On barbiturates, it is surprising that no reference is made to recent work on cerebral metabolism or dystrophia myotonica.

Despite the intention to get the book into print without delay, the text was written during the first 3 months of 1978 and has not reached the reader until more than a year later. This is a disappointment which may not auger well for future volumes in the series. There is no doubt that an up to date review of this size can be most helpful. This particular book is pleasant to read, and sensible, but patchy.

James Parkhouse

Cardiac Anesthesia. Edited by Joel A. Kaplan. Published (1979) by Grune & Stratton, New York. Pp. 530; illustrated; indexed. Price $44.75.

Rarely has the reviewer had the pleasure of reading a textbook which with such clarity of text and illustration fulfils its stated aim. The editor, Dr J. A. Kaplan of the Emory University School of Medicine, Atlanta, Georgia, seeks to contribute to the improvement of anaesthesia for patients undergoing surgery for cardiac disease and if those involved in this aspect of anaesthesia read his book, as they should, then he is likely to succeed.

Although this textbook is aimed primarily at the anaesthetist involved in cardiac surgery, there is much information and sound guidance for all anaesthetists dealing with patients with cardiac disease coming to surgery for other coincidental complaints. Thirteen authors contribute to provide a comprehensive account of the subject ranging from preoperative assessment through premedication to postoperative intensive care. Despite the number of authors, the treatment and style are uniform and there is no needless repetition, a tribute to an expert editor. This is partly achieved, no doubt, by the fact that almost all the contributors come from the same cardiothoracic centre and the book is a distillation of their continued experience.

The text is organized in four main sections—pharmacology and monitoring, disease entities and anaesthesia, cardiopulmonary bypass technique and postoperative care—which makes for ease of reference. It is a mine of information with an extensive and up-to-date bibliography and useful index. It is without doubt the best available text in this field and is certain to become essential reading for all cardiac anaesthetists and a reference book for other anaesthetists dealing regularly with patients suffering from cardiac disease.

Donald Campbell

Medical Acid–Base Balance. The Basic Principles. By M. L. G. Gardner. Published (1978) by Baillière Tindall. Pp. 125; illustrated; indexed. Price £3.95.

Understanding acid–base balance is not easy, if only because so many variables need to be considered in its regulation, its pathophysiology, its significance and its treatment. In this book Dr Gardner describes the physio–chemical background, the physiological regulation, the clinical disturbances and the principles of the relevant clinical measurement.

As always with discussion of acid–base balance, not all will agree with every detail, but the book provides a useful review for those taking the Primary examinations who need more than is available in the standard textbooks.

John Norman

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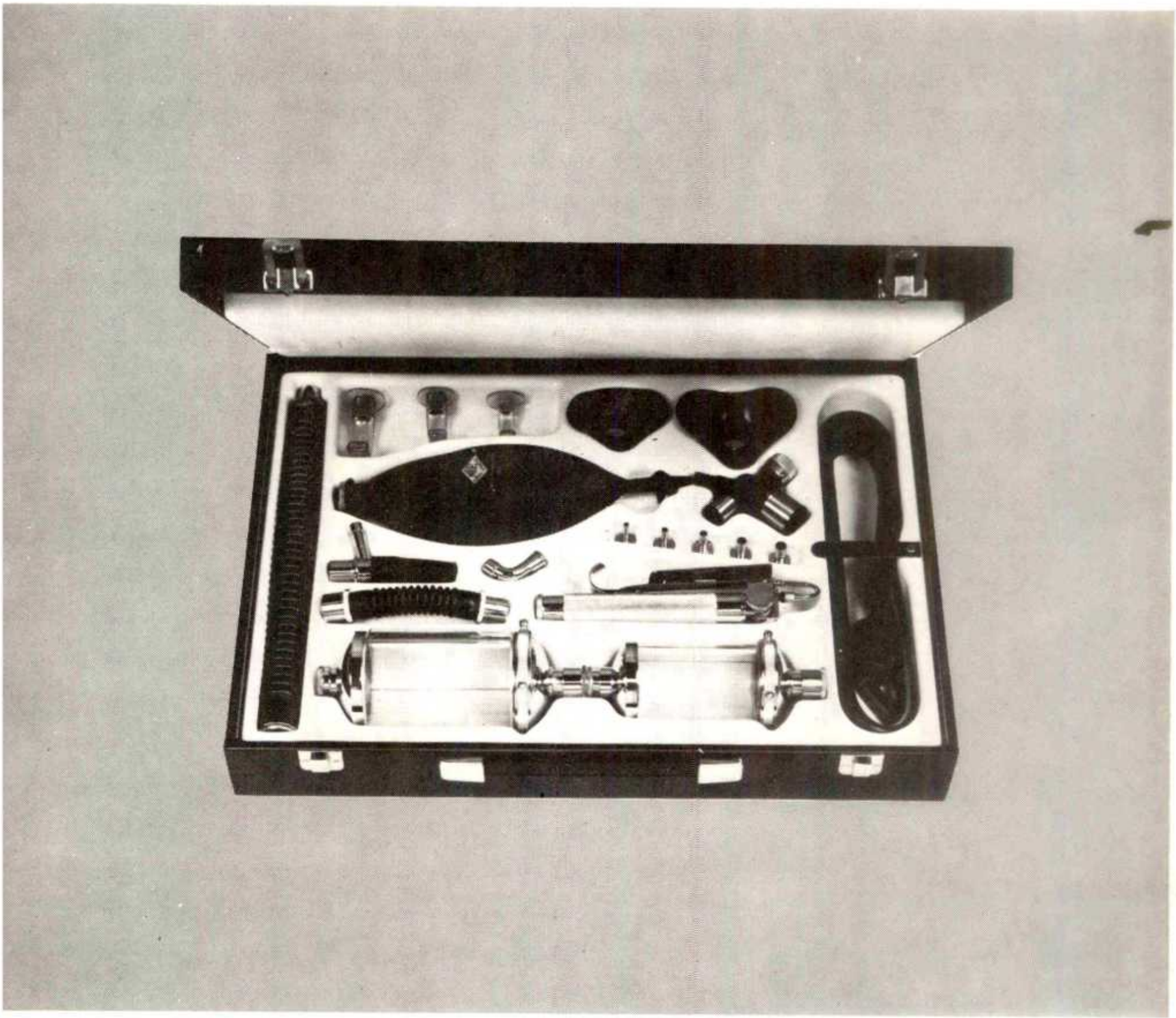

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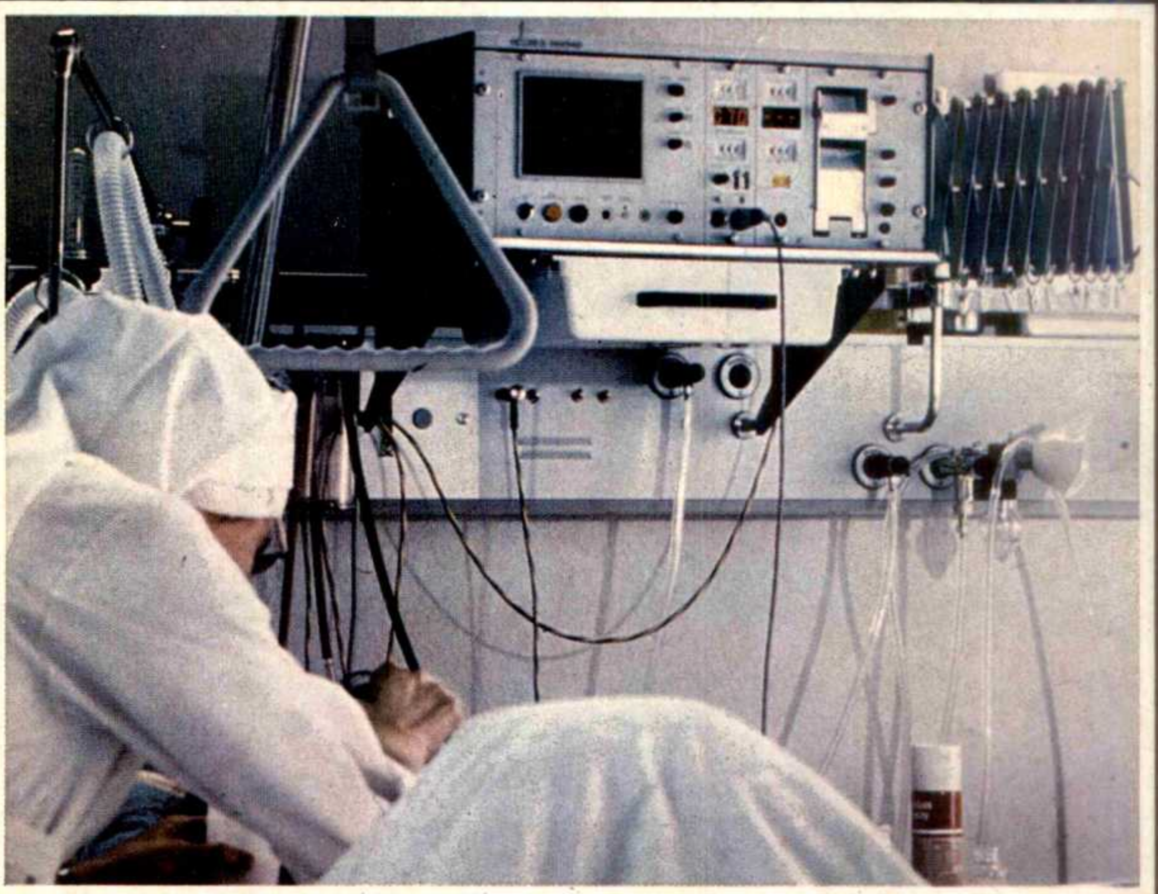

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The GUIDE TO CONTRIBUTORS can be found on pages x, xii & xiv of the advertisement section of this issue.

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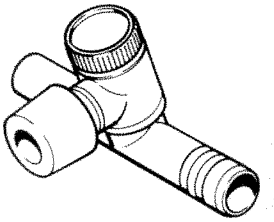

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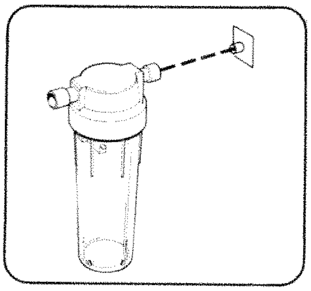

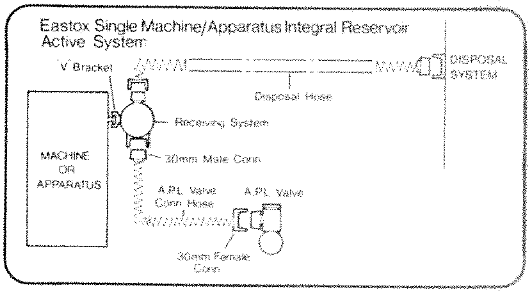

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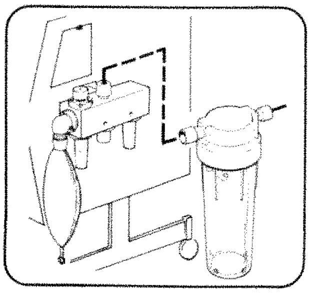

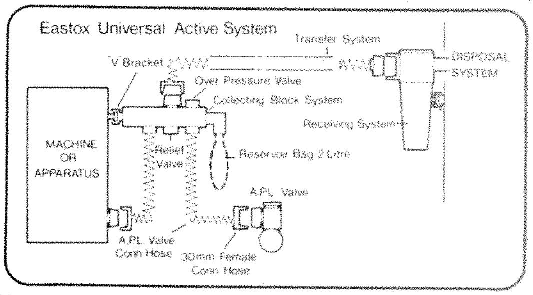

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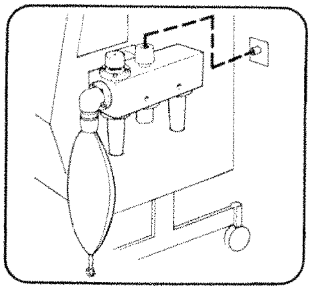

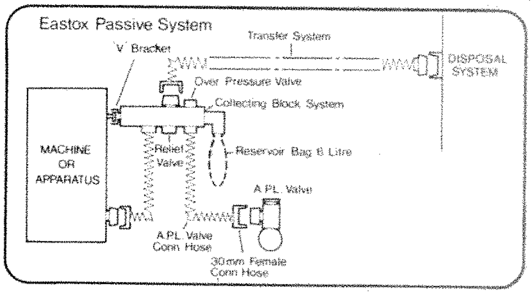

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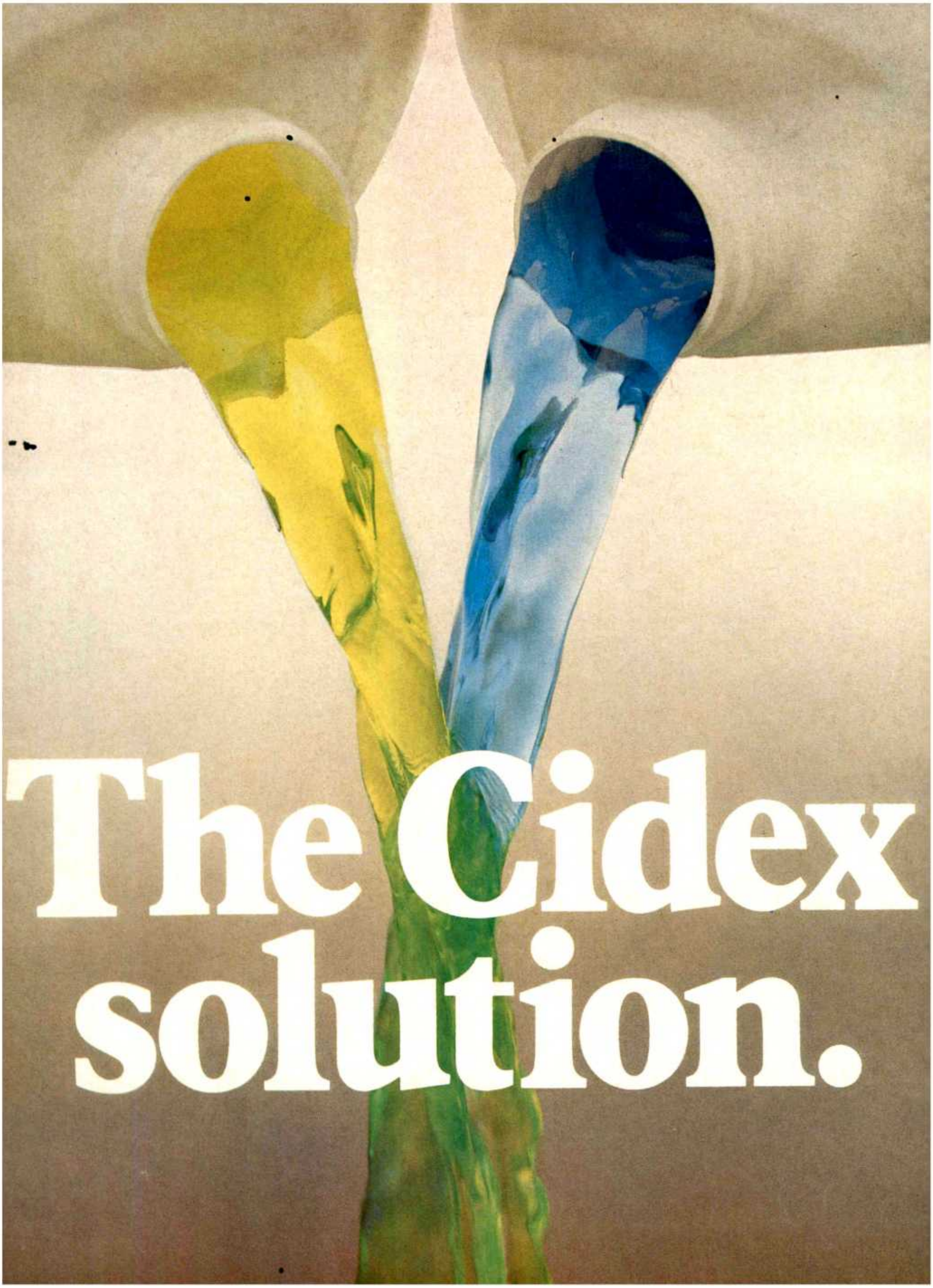
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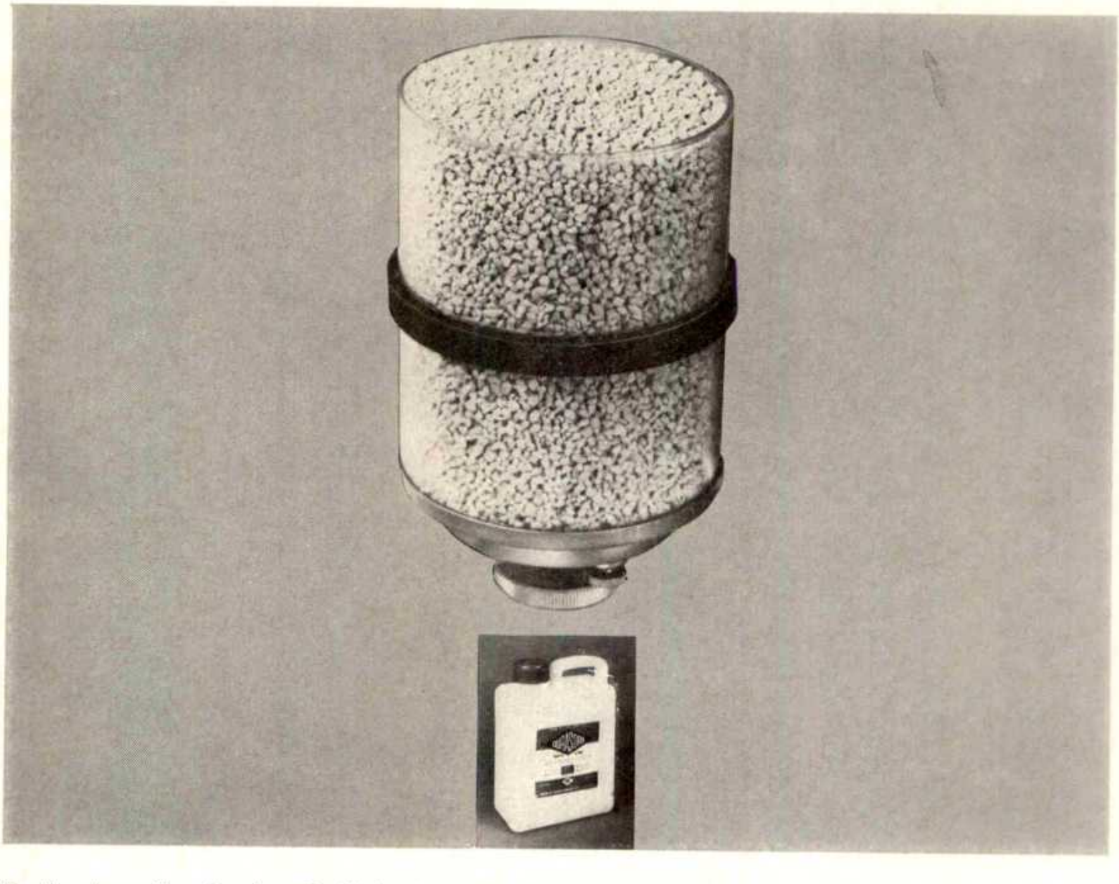

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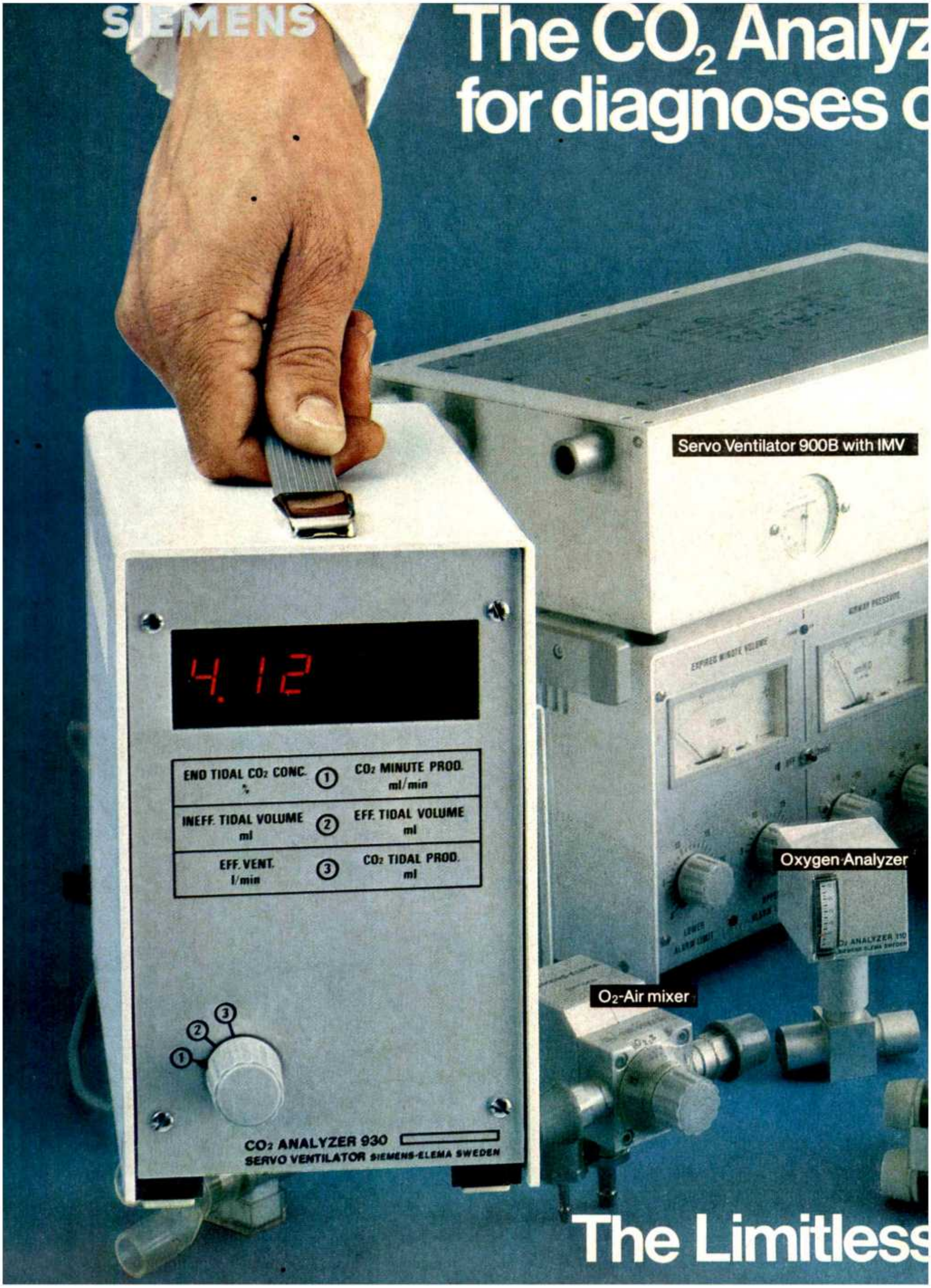

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The summary will be printed at the beginning of the paper. It should be on a separate sheet, in the form of a single paragraph which gives a succinct account of the problem, the methods, results and conclusions, and normally should be of 50–150 words. It may be used as it stands by abstracting journals.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the experiments to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the generic or official name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

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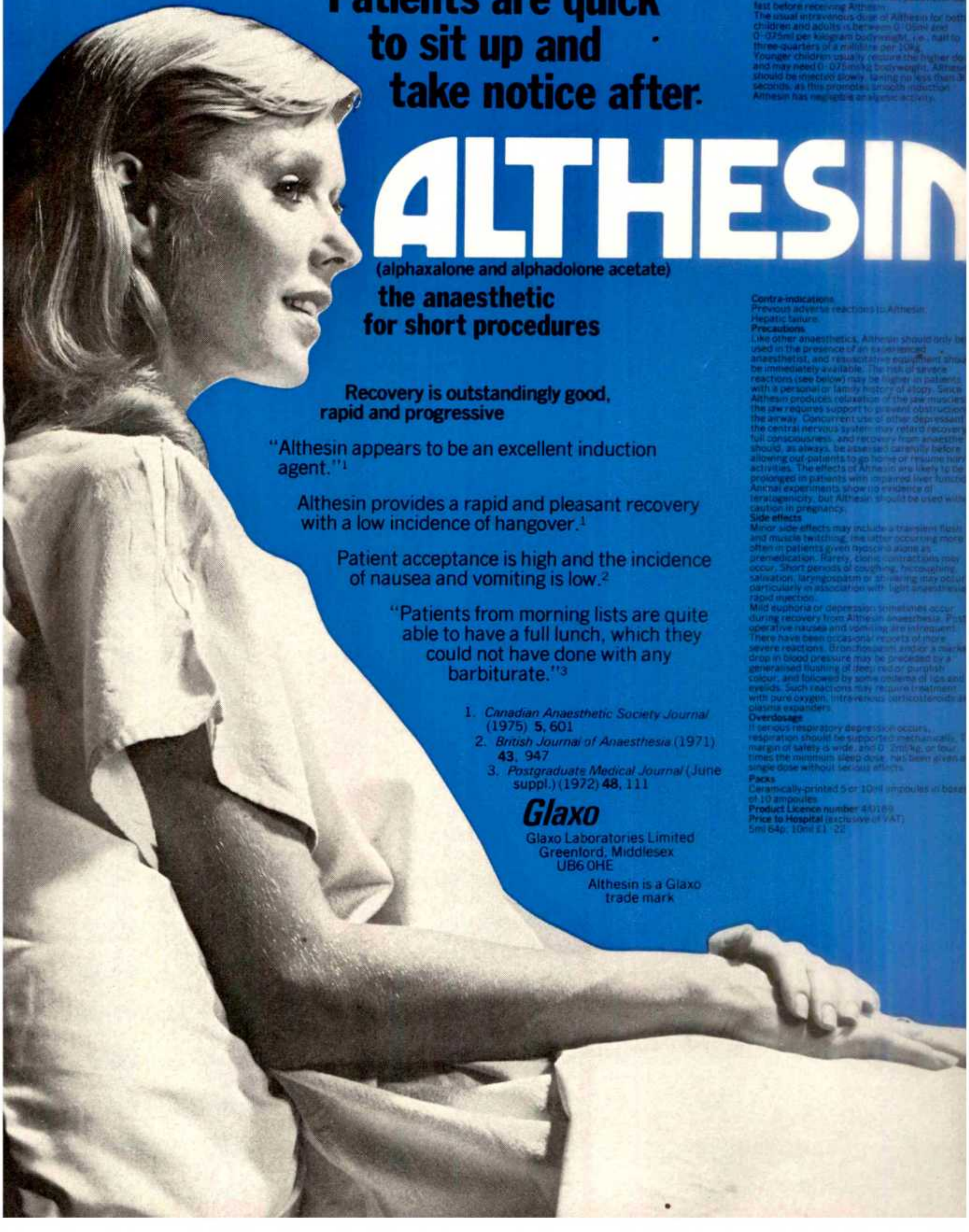

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2. *British Journal of Anaesthesia* (1971) **43**, 947
3. *Postgraduate Medical Journal* (June suppl.) (1972) **48**, 111

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Uses

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Experience is insufficient at present to advocat use of Althesin in infants under one year, in patients with hepatic dysfunction, and for maintenance of anaesthesia in obstetrics.

Dosage and administration

As usual, it is recommended that patients shou fast before receiving Althesin.

The usual intravenous dose of Althesin for both children and adults is between 0·05ml and 0·075ml per kilogram bodyweight, i.e., half to three-quarters of a millilitre per 10kg. Younger children usually require the higher do and may need 0·075ml/kg bodyweight. Althesi should be injected slowly, taking no less than 3 seconds, as this promotes smooth induction. Althesin has negligible analgesic activity.

Contra-indications

Previous adverse reactions to Althesin. Hepatic failure.

Precautions

Like other anaesthetics, Althesin should only be used in the presence of an experienced anaesthetist, and resuscitative equipment shou be immediately available. The risk of severe reactions (see below) may be higher in patients with a personal or family history of atopy. Since Althesin produces relaxation of the jaw muscles the jaw requires support to prevent obstruction the airway. Concurrent use of other depressant the central nervous system may retard recovery full consciousness, and recovery from anaesthe should, as always, be assessed carefully before allowing out-patients to go home or resume norm activities. The effects of Althesin are likely to be prolonged in patients with impaired liver functio Animal experiments show no evidence of teratogenicity, but Althesin should be used with caution in pregnancy.

Side effects

Minor side effects may include a transient flush and muscle twitching, the latter occurring more often in patients given hyoscine alone as premedication. Rarely, clonic contractions may occur. Short periods of coughing, hiccoughing, salivation, laryngospasm or shivering may occur particularly in association with light anaesthesia rapid injection.

Mild euphoria or depression sometimes occur during recovery from Althesin anaesthesia. Post operative nausea and vomiting are infrequent. There have been occasional reports of more severe reactions. Bronchospasm and/or a marke drop in blood pressure may be preceded by a generalised flushing of deep red or purplish colour, and followed by some oedema of lips and eyelids. Such reactions may require treatment with pure oxygen, intravenous corticosteroids a plasma expanders.

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The discussion should not merely recapitulate the experimental results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

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There should be a table of references at the conclusion of the paper. These references should be arranged according to the Harvard system and in alphabetical order. In the text, the year of publication must follow the author's name, more than one paper in any year being indicated by a small letter (a, b, c,) after the date. In the references, the order should be author's name, followed by initials; year of publication in parentheses; title of paper to which reference is made; title of publication underlined with a single line (to indicate italics) and abbreviated in accordance with *Cumulative Index Medicus*; volume number in arabic numerals, underlined with a wavy line (to indicate bold face); the number of the first page in arabic numbers; thus Clarke, M., Evans, D. W., and Milstein, B. B. (1971). Long-term pacing with an inductive coupling system. *Br. Heart J.*, **33**, 65.

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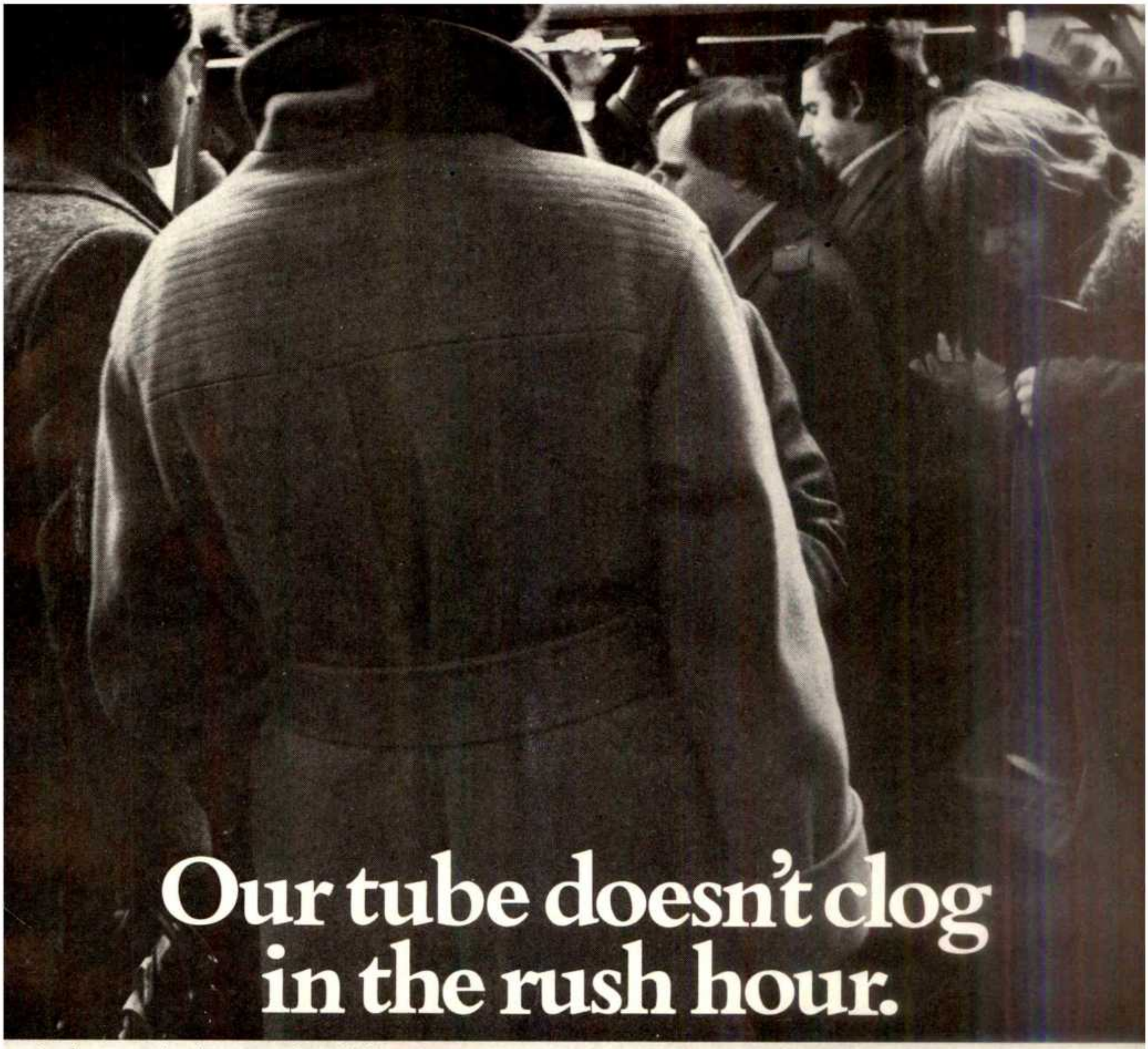

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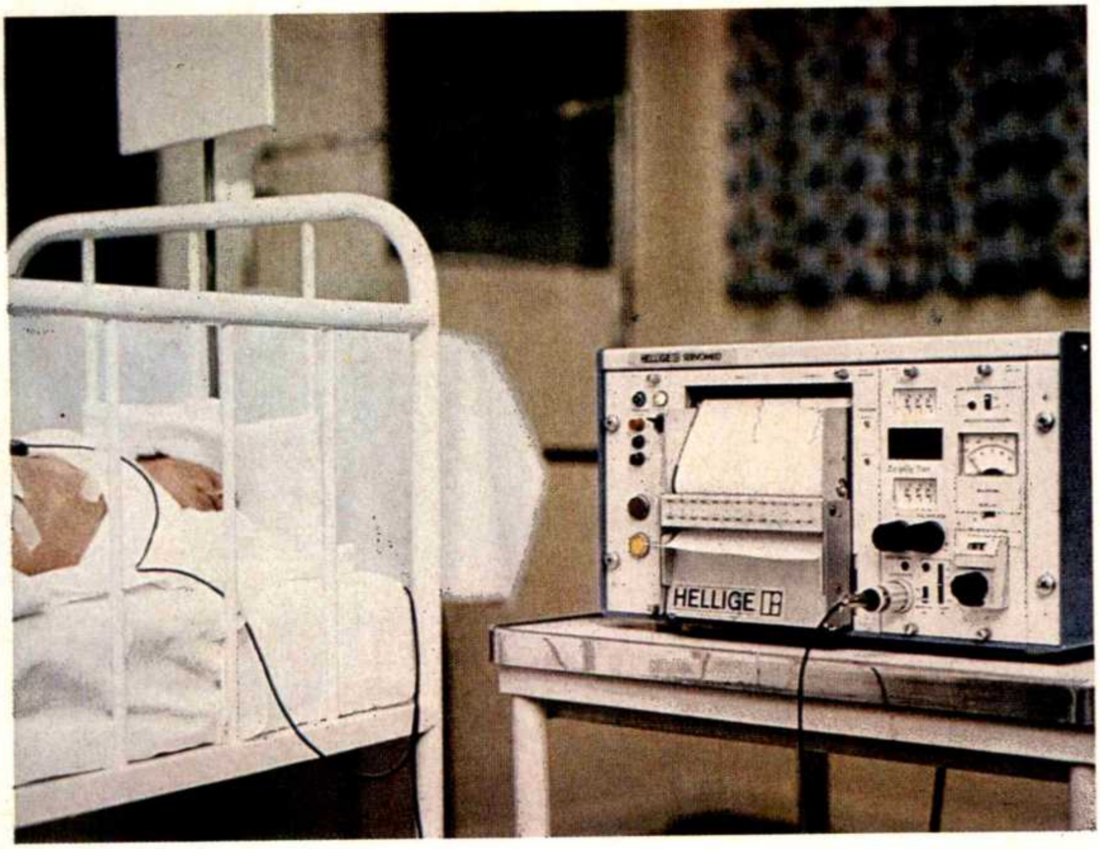

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References
1. Bistrian, B.R., Blackburn, G.L., Vitale, J., Cochran, D., and Naylor, J. (1976). Prevalence of malnutrition in general medical patients. Journal of American Medical Association, 235, 1567-1570.
2. Hill, G.L., Pickford, I., Young, G.A., Schorah, C.J., Blackett, R.L., Burkinshaw, L., Warren, J.V., and Morgan, D.B. (1977). Malnutrition in surgical patients – An unrecognised problem. Lancet, *i*, 689-692.
3. Daly, J.M., Vars, H.M., and Dudrick, S.J. (1972). Effects of protein depletion on strength of colonic anastomoses. Surgery Gynec. Obstet., *134*, 15-21.
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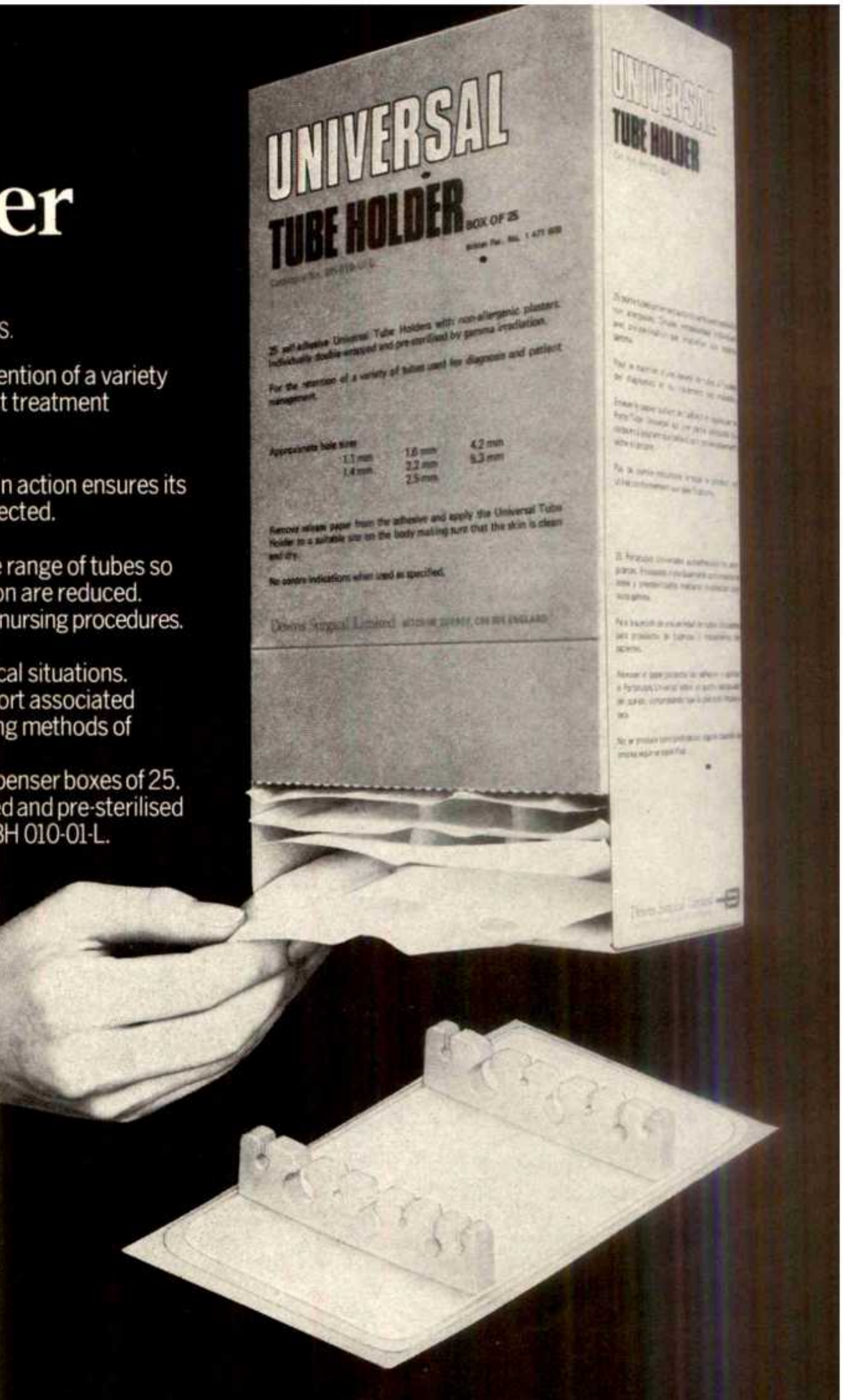

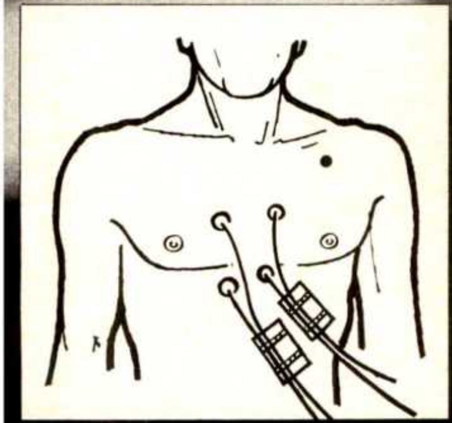

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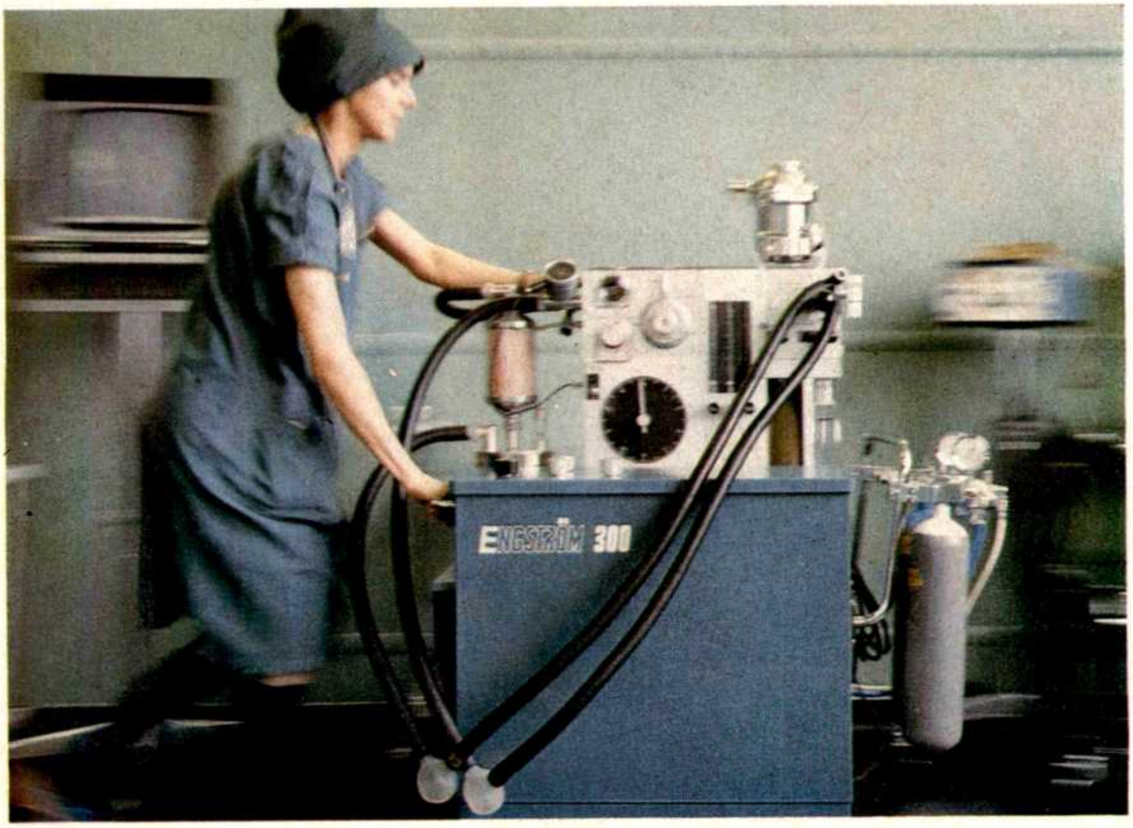

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Dosage and administration Intralipid 10%: 500–1,500 ml daily in conjunction with intravenous amino-acids. For increased caloric requirements Intralipid 20%: 500–1,500 ml daily in conjunction with amino-acids. Intralipid 10% and 20% are administered by slow intravenous infusion. During the first 10 minutes the drip rate should be adjusted to 20 drops per minute and after half an hour this can be adjusted to a final rate of 60 drops per minute. 500 ml of either emulsion should be given in not less than three to five hours on the first day of infusion. On the first day of infusion it is advisable to administer 10 ml Intralipid 10% or 5 ml Intralipid 20% per kg body weight. Subsequently the dose is usually doubled, and when a larger intake is indicated it may be increased to 3 g fat per kg body weight.

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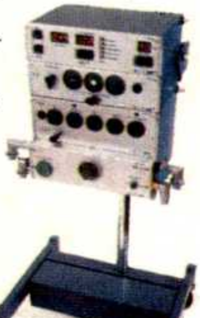

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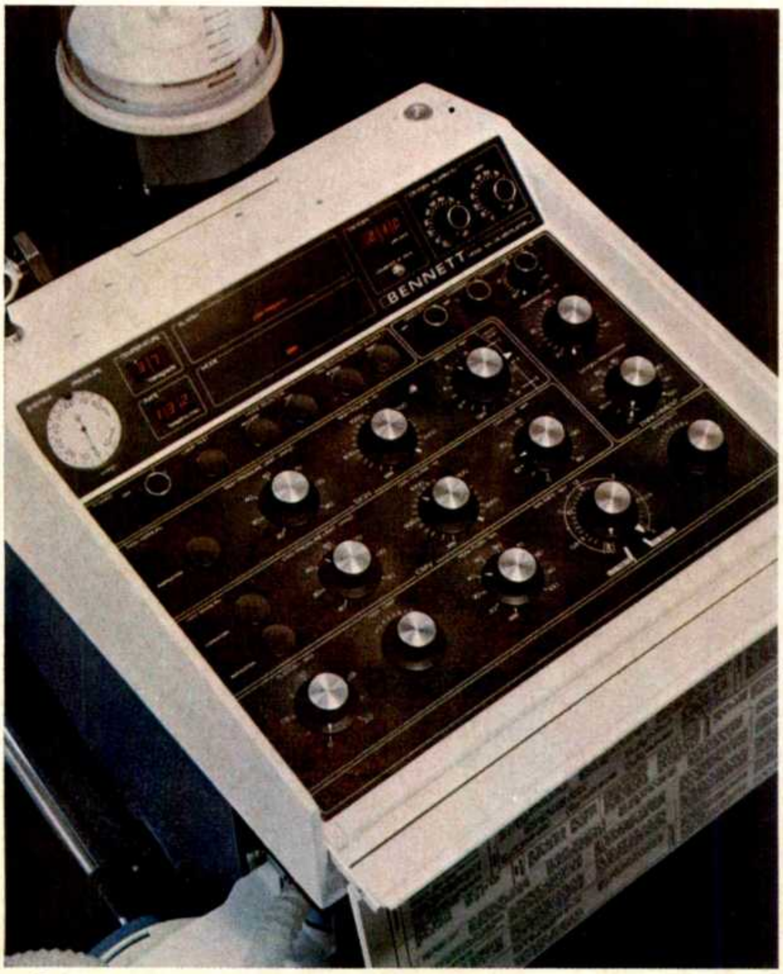

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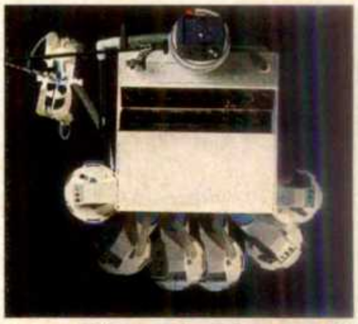

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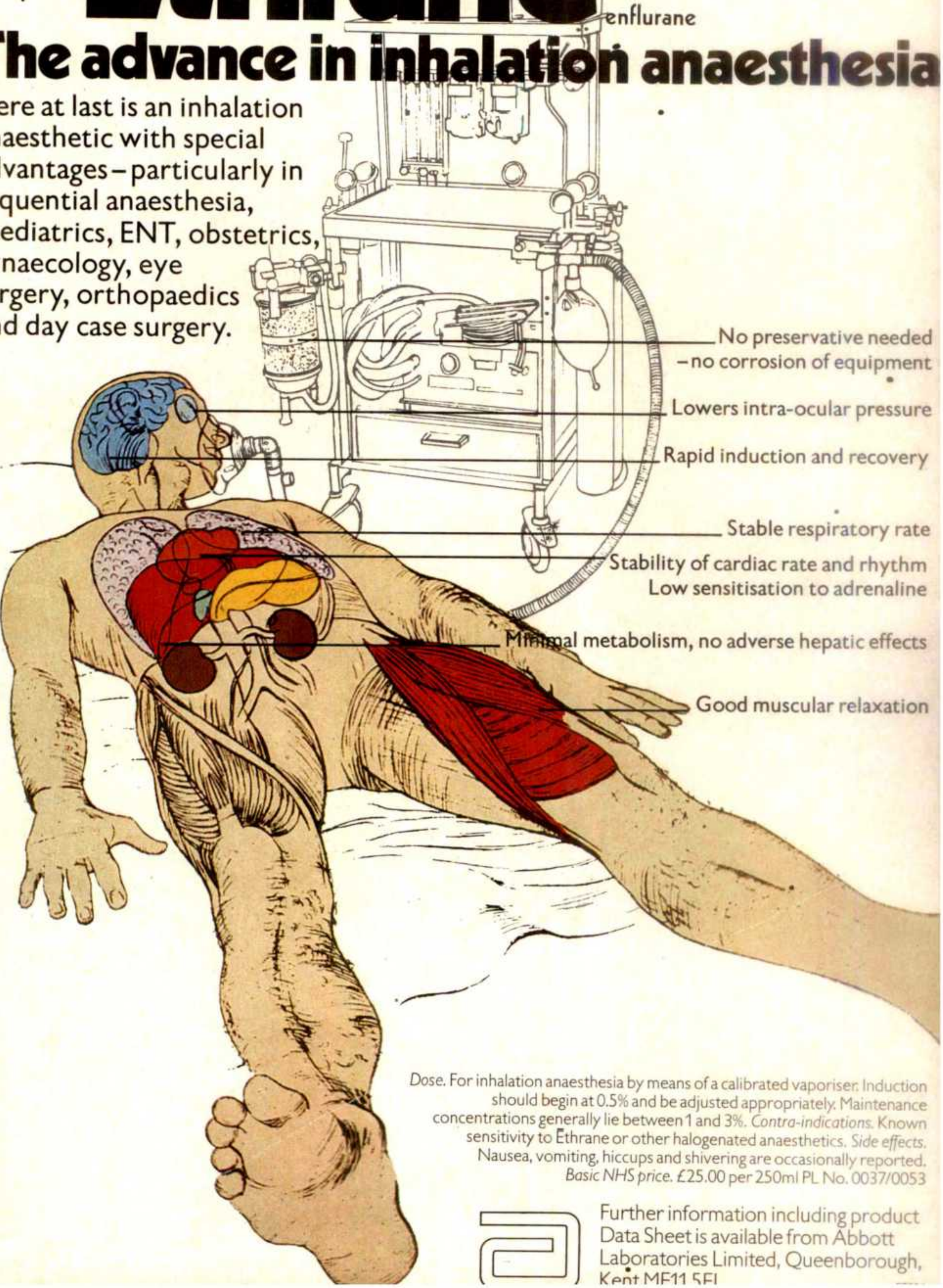
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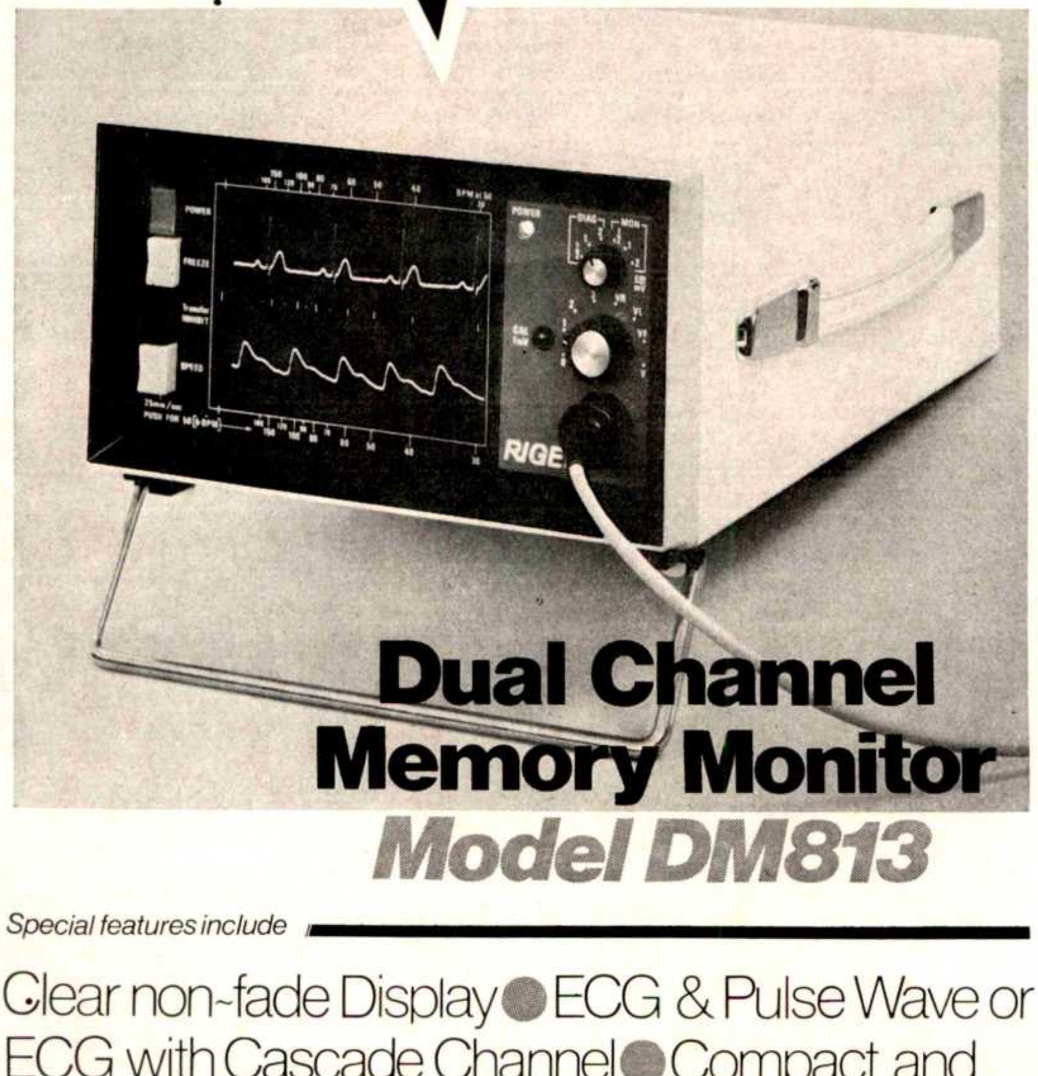

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EDITORIAL

LIVER DYSFUNCTION AFTER REPEATED ANAESTHESIA

Reversible minor changes in liver function are common in the period immediately after operation. The relative contributions of anaesthesia and surgery to these changes cannot be quantified easily in man. However, indirect evidence from animal and human studies suggests that pre-existing liver dysfunction, hypoxia, hypotension and hypercarbia, surgical trauma and interference with liver blood flow, viral hepatitis as well as hepatotoxic effects of anaesthetic and other drugs are important factors. With regard to halogenated volatile anaesthetic agents, a spectrum of hepatotoxicity may be imagined, ranging from chloroform as "worst" to enflurane as "best" with halothane somewhere in between. Hepatotoxicity may be enhanced in animal models by enzyme induction and in the case of halothane by stimulation of the reductive pathway (Van Dyke and Gandolfi, 1976). This mode of metabolism of halothane has been postulated as the mechanism of halothane-associated hepatitis in man (Cohen et al., 1975).

Neither the aetiology nor the frequency of halothane-associated hepatitis has been established in man. However, the condition appears to be rare and frequencies ranging from 1 in 6000 to 1 in 110 000 anaesthetics have been suggested (Inman and Mushin, 1974; Bottinger, Dalen and Hallen, 1976). In addition, the condition is most commonly associated with repeated exposure to halothane at short intervals of time, usually within 4 weeks (Inman and Mushin, 1974; Walton et al., 1976). The liver dysfunction described by these authors included jaundice and a high frequency of fulminant hepatic failure. In addition, various markers of immunological processes, indicating that an immune reaction may be involved in the development of halothane hepatitis, have been found in clinical studies (Walton et al., 1976; Vergani et al., 1978). The most striking feature of halothane hepatitis is its sporadic nature and the severity of the liver dysfunction, which is out of all proportion to the anaesthesia and surgical procedure which have preceded its development. There seems little evidence to support the concept of a pyramid of problems—a large number of patients with mild hepatic dysfunction at the base with a few patients at the peak with severe problems (Strunin, 1977). Studies of halothane metabolism in man (Sharp, Trudell and Cohen, 1979) indicate that reductive as well as oxidative metabolism may occur in normal individuals without enzyme induction or hypoxia. If this is so, then it is less likely that the reductive pathway is primarily responsible for liver cell damage, and other mechanisms such as hapten formation leading to an immune response may be necessary. This would fit with the lack of dose-response and the association of repeated exposure found in cases of unexplained hepatitis associated with halothane (Walton et al., 1976).

Against this background, how can we view the prospective study by Fee and his colleagues in the present issue of the Journal? First, the number of patients studied is small and therefore it is unlikely, except by chance, that the halothane group would include a patient who was likely to develop halothane hepatitis as described above. This has indeed been the case: none of the patients given halothane appears to have come to any harm, or developed jaundice or eosinophilia or other signs of clinical liver dysfunction. All the changes were confined to alterations in enzyme concentrations. Second, most of the patients received their second halothane anaesthetic at more than a 4-week interval and the number of patients receiving more than two exposures to halothane in this period is so small as to make interpretation of the results obtained difficult. A factor adding to this difficulty is the use in some tables of logarithmic transformation of enzyme concentrations. Although this may be correct with regard to the known skewing of the distribution of some enzyme concentrations in the population, it is not normal practice in most laboratories. Therefore, this may lead to confusion if attempting to compare the Belfast figures with those obtained in other centres.

The major findings of the Belfast study are contained in tables VI and VII. These ostensibly show an increasing percentage of abnormalities in enzyme concentrations with increasing numbers of exposures to halothane (table VI), whereas there are only minor changes in the patients who received enflurane (table VII). The difference between halothane and enflurane is not unexpected, but the magnitude of the changes seen with halothane needs some further elucidation. On enquiry from the authors it was ascertained that all changes use the first value obtained before the first anaesthetic as a reference point. In addition, it is not necessarily the same patients who show abnormalities after each anaesthetic. Furthermore, in some patients the increased concentrations had not returned to the pre-first anaesthetic concentration before a further anaesthetic was administered. No unethical behaviour is implied, since the results were not available to the anaesthetist concerned. Although all the information is now available analysis has not yet been completed. It is possible, therefore, that the majority of the changes in the halothane group may be confined to a few patients who should be considered in more detail. In particular, those patients whose enzymes had not returned to normal before receiving further halothane are of special interest. It has been suggested by Trowell, Peto and Crampton-Smith, (1975) that transaminase screening before operation would be of value in identifying patients prone to develop halothane hepatitis. The present study may have contributed to the view that such enzyme screening is of little help.

Can any conclusions be drawn from the study by Fee and his colleagues? There were more abnormal changes in enzyme activities associated with halothane than with enflurane. This concurs with animal studies, but would need further confirmation in man as the number of patients studied here is small. Whether the changes associated with halothane are of any relevance is a matter for debate. In the present study they clearly had no effect on the outcome as none of the patients showed any overt signs of liver dysfunction. Nevertheless, there is concern about repeatedly exposing patients to halothane and the possibility of a severe liver reaction occurring. Such hepatitis following enflurane anaesthesia has not been reported in the literature, although there are isolated case reports of minor liver dysfunction. Many anaesthetists would welcome an alternative to halothane for those patients where repeated anaesthesia is required. In the present study care was taken to use halothane-free anaesthetic machines and operating areas during enflurane administration, but this is not a practical proposition for most anaesthetic departments. The cost of the Belfast study both in time and manpower has been immense, whereas the information gathered is limited to simple measurements of some aspects of liver function. Attempting to analyse the results by comparison with other similar studies (McEwan, 1976; Allen and Downing, 1977; Thompson and Friday, 1978) shows that there is considerable disagreement with respect to the effects of halothane. This lends support to the suggestion that assessing liver function after operation by changes in transaminases (or related enzymes) alone is unrewarding (Strunin, 1978). Until the mechanism of liver damage associated with halothane has been elucidated it is unlikely that a specific test will become available. In the meantime, one wonders whether further studies along the lines of Fee and his colleagues can be justified.

Leo Strunin

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HALOTHANE DOES NOT INHIBIT HUMAN NEUTROPHIL FUNCTION *IN VITRO*

J. F. NUNN, J. E. STURROCK, A. J. JONES, C. Ó'MORÁIN,
A. W. SEGAL, S. B. COADE, J. DORLING AND D. WALKER

SUMMARY

Various indices of function of neutrophils from normal healthy volunteers have been examined after *in vitro* exposure to halothane. Random free movement on glass was unaffected, but random migration through millipore filters was slightly increased. There was no significant change in migration in response to casein chemotaxis. Phagocytosis, degranulation and the enhanced non-mitochondrial respiration associated with phagocytosis were unaffected. Electron-microscopic appearance at 30 s after exposure to latex particles was normal in all respects.

The review of Moudgil and Wade (1976) summarizes the conflicting evidence on the effect of anaesthetic agents on the course of an infection. One aspect of the problem is the effect of anaesthetics on the function of polymorphonuclear neutrophils and there is considerable uncertainty in this field. *In vivo* studies were reported by Bruce (1966, 1967), who found that the accumulation of intra-peritoneal neutrophils in mice, provoked by an intra-peritoneal injection of pseudomonas endotoxin or live *Salmonella typhimurium*, was reduced by halothane anaesthesia during the time that extravasation should have been occurring. There was also evidence of impaired *in vivo* phagocytosis of *Salmonella*.

Cullen, Hume and Chretien (1975) studied phagocytosis *in vitro* by neutrophils extracted from blood samples withdrawn from patients anaesthetized with either halothane and nitrous oxide, or nitrous oxide–thiopentone–fentanyl–droperidol. Both types of anaesthesia caused only minimal depression of phagocytosis of latex particles and also of neutrophil enzymatic reduction of nitroblue tetrazolium (NBT), which normally occurs during phagocytosis of bacteria or latex particles (Baehner and Nathan, 1968; Park, Figrig and Smithwick, 1968). Stanley and others (1976) also studied blood withdrawn from anaesthetized patients and reported reduced chemotactic index and random migration of neutrophils, which were restored almost to normal in samples withdrawn after surgery had commenced. Lecky and others (1974) administered 70% nitrous oxide, tubocurarine and morphine to volunteers and examined their white cells in blood samples. They found no effect on phagocytosis of latex particles, but a significant decrease of NBT reduction. Total white cell counts and absolute neutrophil counts were increased. Hill and others (1978) used 60% nitrous oxide and morphine on volunteers and found a significant increase in neutrophil chemotaxis in blood samples, but no effect on neutrophil or total white cell counts. Most of the anaesthetic would have been lost during the extraction of the neutrophils from these blood samples drawn from anaesthetized patients.

Studies of the effect of anaesthetics administered *in vitro* on neutrophil motility do not appear to have been reported, and studies of chemotaxis have produced contradictory results (Duncan and Cullen, 1977; Moudgil et al., 1977). *In vitro* phagocytosis of latex particles by human neutrophils was scarcely affected by incubation of the cells with gas mixtures containing 2.5% halothane (Cullen, 1974). Rosenbaum and Orkin (1973) also found no *in vitro* depression by halothane of phagocytosis of yeast particles by human neutrophils.

The work summarized above leaves us in some doubt as to whether anaesthetic agents themselves have a significant effect on neutrophil function. We have therefore undertaken a series of experiments on these cells, which were extracted from venous blood of normal human subjects and subsequently equilibrated with anaesthetic gas mixtures *in vitro*. We have studied random free movement, chemotaxis in response to casein, oxygen consumption of the

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neutrophils after phagocytosis of latex particles, and electron microscopy of cells exposed to these particles to assess ingestion and degranulation, and to examine their general morphology.

METHODS

Random free movement on glass

One drop of capillary blood from a normal human subject was incubated at 37 °C on a 22-mm diameter circular glass cover-slip for 30 min. The clot was then washed off with saline, leaving the neutrophils adherent to the glass (Harris, 1953). The cover-slip was mounted as one wall of a modified Rose chamber, which was filled with Eagle's minimum essential medium, containing 10% fetal calf serum, previously equilibrated with 5% carbon dioxide in air. Movements of neutrophils were recorded by time-lapse cine-micrography (one exposure per 2.5 s) using a ×40 objective and phase-contrast illumination. The entire experiment was conducted in a hot room maintained at 37 °C. Three experiments were carried out, the third with calcium-free medium.

A control period was maintained for 1 h, during which a further batch of 30 ml of medium was equilibrated in an Adam's tonometer with 2% halothane, vaporized in 5% carbon dioxide in air, for at least 30 min. The Rose chamber was then flushed with 27 ml of medium equilibrated with halothane and sealed for 30 min, during which filming continued. Finally, the chamber was flushed with a fresh 27 ml of medium equilibrated with 5% carbon dioxide in air, and then sealed for a further 35 min to allow study of recovery.

Movements of the neutrophils were analysed by single frame projection, using a Spectro analysing projector. Movement was quantified in two ways. First, we recorded the distance travelled (μm) by the centre of the most prominent nuclear lobe in each cell as the sum of the distances travelled in successive periods of 25 s for a total duration of 5 min 25 s or 12 min 30 s (time being determined by the requirement to have at least five cells remaining within the field). Second, we determined the ratio of the total area covered by the cell in 21 min to the initial surface area of the cell. In each case, quantification covered the period immediately before changing the medium.

Phagocytosis

It is virtually impossible by light microscopy to distinguish between particles which have been phagocytosed and particles which are merely adherent to the surface of a cell. We have therefore employed electron microscopy.

Venous blood was drawn into heparin 5 i.u. ml^{-1} from healthy volunteers and erythrocytes were sedimented with 1% dextran 500 (Pharmacia). Neutrophils were separated from the supernatant plasma by density centrifugation (Boyum, 1968) freed of residual erythrocytes by hypotonic lysis and then suspended in RPMI 1640 medium (Flow Labs, Irvine) containing heparin 5 i.u. ml^{-1}.

Two millilitre of neutrophil suspension was equilibrated with 2% halothane, vaporized in air, by bubbling at a flow rate of approximately 10 ml min^{-1} for 30 min in a conical test tube suspended in a water-bath maintained at 37 °C. Polystyrene-latex particles (0.5 ml of a suspension, Difco 0.81 μm diameter, 1×10^{10} ml^{-1}), opsonized with human IgG (Segal and Coade, 1978), were then added and the mixture was stirred for 30 s before stopping phagocytosis by the rapid addition of 2.5% glutaraldehyde in phosphate buffer 0.1 mol litre^{-1} at pH 7.4 containing magnesium chloride 0.02 mol litre^{-1} at 0 °C. The cells were transferred to a larger volume of fixative and fixation was allowed to proceed for 1 h at 0 °C. After thorough washing with phosphate buffer containing magnesium chloride, the cells were post-fixed in 1% osmium tetroxide in phosphate 0.1 mol litre^{-1} at pH 7.4, for 1 h at room temperature. After a brief rinse in phosphate buffer, they were centrifuged through melted 2% agar, cooled, chopped into small cubes and embedded in Araldite by a standard procedure. Ultrathin sections were stained with uranyl acetate and lead citrate before examining in an A.E.I. EM 6B electron microscope.

Oxygen consumption

Neutrophil suspensions were prepared as described above and diluted to a cell number of 2×10^7 ml^{-1}. Aliquots of 3.5 ml were equilibrated with different concentrations of halothane in air, ranging from 0.5% to 3.0%. Simultaneous controls were equilibrated with air. After 30 min of equilibration, 3 ml of the suspensions were transferred to a closed, rapidly-stirred, thermostatically-controlled plastic chamber, maintained at 37 °C, containing a Clark-type polarographic electrode. After thermal equilibration, when a slowly decreasing Po_2 was recorded, 0.25 ml of a suspension of latex particles (as described above) was added without exposure of the neutrophil suspension to air. The subsequent decrease in Po_2 was recorded on a chart recorder (Segal and Coade, 1978). The polarograph was calibrated with air-equilibrated water and the zero was determined with sodium dithionite.

Control of halothane concentrations

Halothane mixtures were dispensed from a Vapor vaporizer (Drager) with a carrier gas flow of 500–800 ml min^{-1}. Surplus effluent gas flow was vented through an interference refractometer for measurement of halothane concentration (Hulands and Nunn, 1970).

Gas chromatography was used to measure the halothane concentrations in neutrophil suspensions at various stages in the experiments. Equilibration with the gas stream was better than 90% complete in 30 min. Transferring the sample to the polarograph could not be completely anaerobic and the loss of halothane was up to 10% of initial value, including the loss into the neoprene O-ring which surrounded the electrode. The latex suspension contained approximately 1% of polystyrene and partitioning of halothane between the cell suspension and the latex particles resulted in a further decrease of halothane partial pressure of about 10%. Taking all factors into account, equilibration with 2% halothane would result in a final halothane partial pressure of about 1.5% of an atmosphere, after transfer of the sample to the polarograph and the addition of latex. We have reported all results in terms of the halothane concentration in the gas mixture with which the neutrophil suspension was originally equilibrated.

In the studies of random motility there was no reason to believe that the partial pressure of halothane was reduced to less than the value of the gas mixture used for equilibration of the medium.

Chemotaxis

Neutrophils from seven healthy volunteers were isolated from heparinized blood by dextran sedimentation and resuspended at 2×10^6 ml^{-1} in Hanks solution adjusted to pH 7.2, but without the addition of albumen or serum. The neutrophil suspension from each volunteer was divided into two equal aliquots. Chemotaxis on the control fraction was carried out during exposure to ambient air at 37 °C. To study the effects of halothane, the second fraction was placed in a glove box at 37 °C which was flushed with 2% halothane vaporized in air at an initial flow of 3 litre min^{-1}, reduced to 1 litre min^{-1} when equilibrium had been obtained. The effluent gas was ducted from the glove box and monitored with a refractometer. The neutrophil suspensions and the Hanks solution and casein were exposed to the halothane for 30 min before the chemotaxis chambers were assembled within the glove box, and exposure to halothane in the glove box was continued throughout the period of incubation. The migration of neutrophils in 0.25 ml of the suspensions through a millipore membrane (3-μm pore size) was measured by a modification of the method described by Aggett and others (1979). Casein 0.5% (Sigma) was the chemotactic factor used. After 3 h incubation the membranes were separated, washed free of red cells, fixed in isopropyl alcohol, washed, stained with haemotoxylin, dehydrated, cleared and mounted on slides. The neutrophil migration from the filter top was measured using the "leading front" method and the mean of five readings of the cell front on each filter was calculated. The assay was done in duplicate, with and without casein, for each volunteer in both fractions (with and without exposure to halothane).

RESULTS

Random free movement

Figure 1 shows the pattern of movement for three typical neutrophils before, during and after exposure to medium equilibrated with 2% halothane. This figure shows the most active cells, which were seen in experiment 3 when using calcium-free medium. No significant differences in the two indices of random movement (total random free walk and area covered) were found for any of the three experiments (figs 2 and 3).

Phagocytosis and degranulation

The morphology of neutrophils exposed to 2% halothane appeared normal when assessed by transmission electron microscopy. Thirty seconds after mixing the cells with latex particles, opsonized with IgG, a considerable number of particles could be seen within the phagocytic vacuoles, and cytoplasmic granules had fused with, and released their contents into, some of these vacuoles (fig. 4). A count of the number of particles within 25 cells, selected at random, showed a mean number of 4.76 (SEM ± 0.55) particles per cell (in the plane of the section) for halothane-treated cells, but only 4.04 (SEM ± 0.55) particles per cell for untreated cells.

Oxygen consumption

Oxygen consumption of six control samples taken over 5 h showed no significant deterioration related to time. The oxygen consumption was linear during the first minute, and showed a mean value of 128 nmol ml^{-1} min^{-1} (SD 31.6).

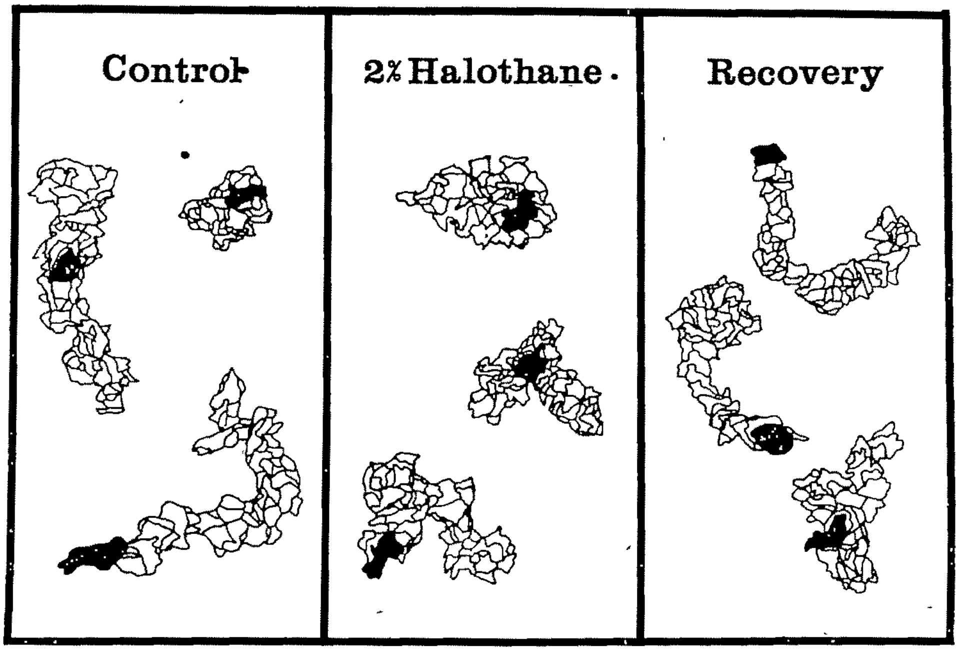

FIG. 1. Tracing of movement of three different neutrophils at intervals of 25 s for periods of 21 min each. Control period, exposure to 2% halothane and recovery.

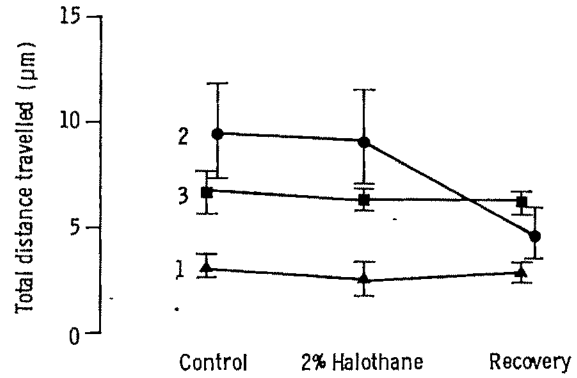

FIG. 2. Random free movement of neutrophils in three experiments, measured as linear movement of the centre of the most prominent lobe of the nucleus at 25-s intervals during 21 min. Bars show mean ± 2 SEM.

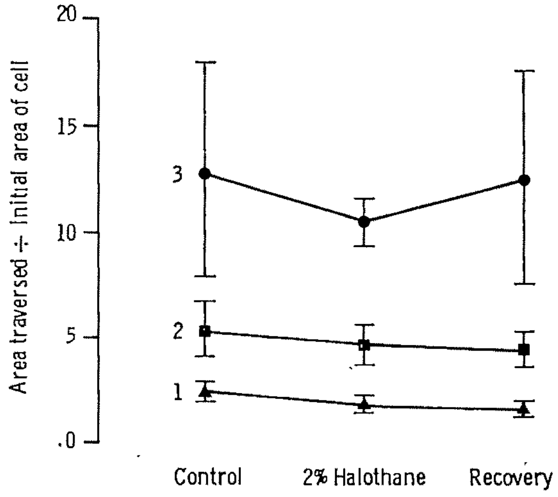

FIG. 3. Random free movement of neutrophils in three experiments, measured as the ratio of the area traversed during 12.5 min to the initial area of the cell. Bars show mean ± 2 SEM.

The lag between injection of latex particles and commencement of linear phase of oxygen consumption was 18–24 s (fig. 5). Equilibration of the neutrophil suspension with halothane had no effect on this lag, and no values for the linear phase of oxygen consumption were more than two standard deviations from the mean oxygen consumption of the controls. Mean values for oxygen consumption at each halothane concentration were all within two standard errors of the mean of the controls (fig. 6). P_{O_2} decreased to close to zero in all cases.

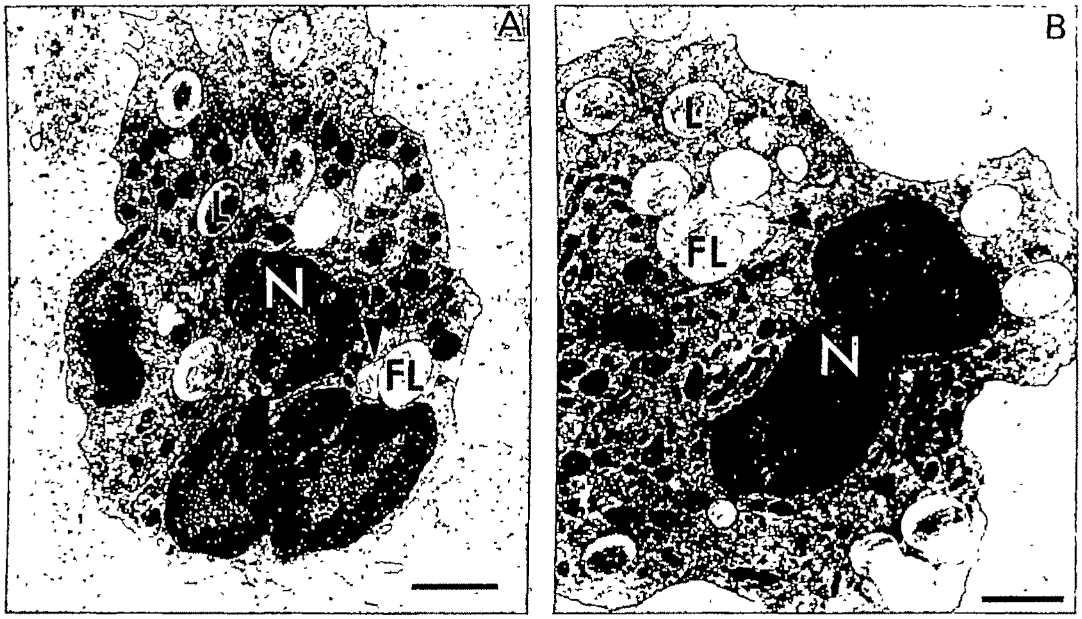

FIG. 4. Halothane treated (A) and untreated (B) neutrophils showing phagocytosed latex particles (L) in vesicles. Some of the cytoplasmic granules have fused with and degranulated into these phagocytic vesicles (FL). The arrows point to the membrane of the fused granules. N = nucleus. Bar = 1 μm.

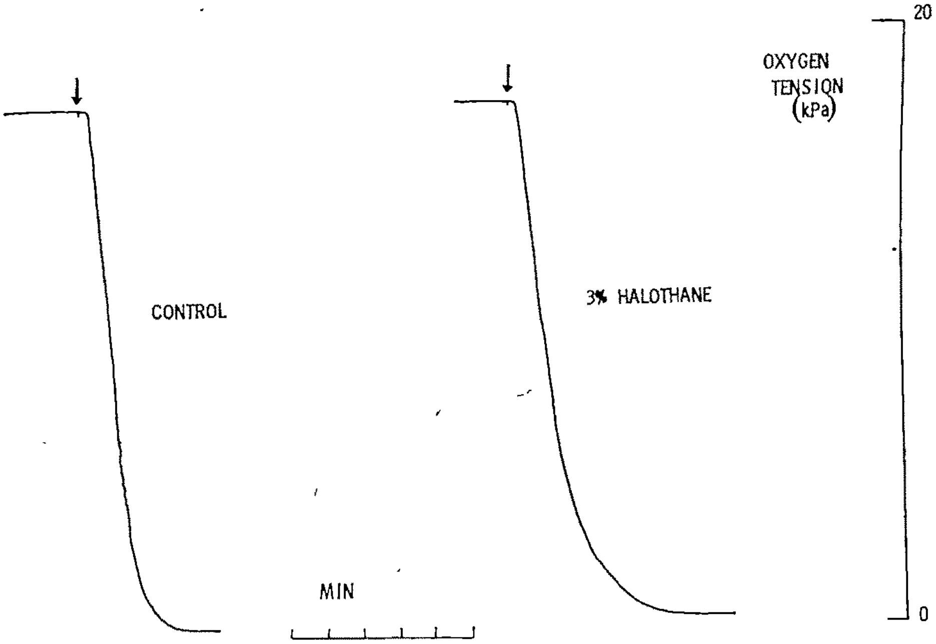

FIG. 5. Uptake of oxygen shown as decrease in Po_2 following addition of a suspension of latex particles opsonized with IgG at the point indicated by the arrows.

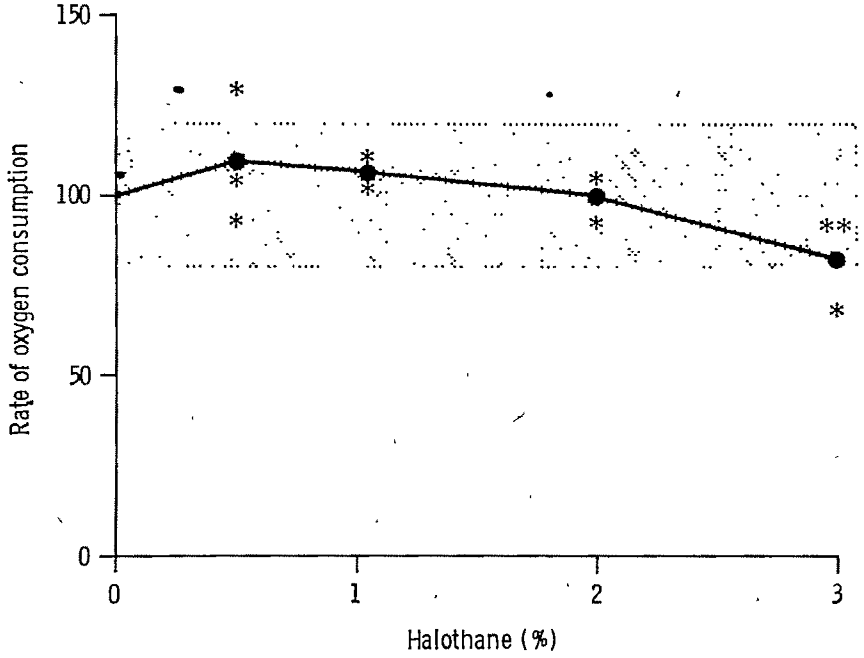

FIG. 6. Maximal rate of oxygen consumption of neutrophils (see fig. 5), exposed to various concentrations of halothane. Oxygen consumption is expressed as a percentage of mean uptake by cells exposed to air (64 nmol 10^{-7} cells min^{-1}). The mean points of the individual measurements at the various concentrations of halothane are shown as black circles and individual measurements as stars. The stippled area indicates mean ±2 SEM of control measurements.

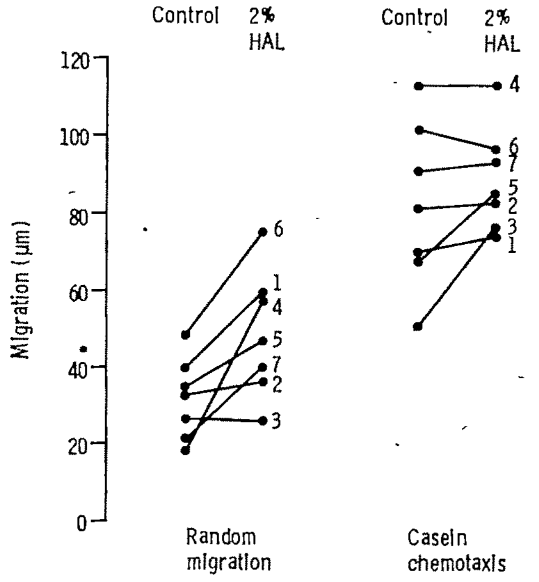

FIG. 7. Distances travelled in 3 h by neutrophils through millipore membranes of 3-µm pore size. The numbers 1–7 represent mean values for neutrophils from seven different subjects.

Chemotaxis

Figure 7 shows mean migration of neutrophils from seven subjects as random movement and also in response to casein chemotaxis. Samples were used as their own controls to compare the migration in the presence of air and in 2% halothane in air. For random movement there was a mean increase of 17.7 µm which was significant (paired Student's t test, $0.02 > P > 0.01$). In response to casein chemotaxis, the mean migration was increased by 6.7 µm, but this was not significant ($t = 1.6$).

DISCUSSION

This study indicates that the incubation of human neutrophils *in vitro* with halothane at concentrations up to 2% did not appear to influence the parameters of function of those cells which were examined, apart from a slight increase in random movement through a millipore filter. Random movement appeared normal, as did the electron microscopic assessment of the morphology of the cells, phagocytosis and degranulation. The enhanced oxygen consumption that followed the addition of latex particles (coated with IgG) to the cell suspension does not result from enhanced mitochondrial respiration (Sbarra and Karnovsky, 1959) but is the result of the production of microbicidal free radicals (Green et al., 1979) by a recently described cytochrome *b* system (Segal and Jones, 1978). This mechanism, too, appears to be quite unaffected by halothane up to concentrations of 3% in the gas phase and it provides evidence of the integrity of a complex co-ordinated process, which includes intact surface receptors for the IgG, phagocytotis, degranulation and function of the bactericidal oxidase system.

The negative results for the effect of halothane on casein chemotaxis are in agreement with the work of Duncan and Cullen (1977), although they used a different chemotactic agent. Like them, we found that the mean rate of migration in response to chemotaxis was actually increased in the presence of halothane, although the difference was not significant in either study. Enhanced activity of neutrophils in the presence of an anaesthetic was first reported by Hamburger (1916), who found that the addition of chloroform ("1 : 20,000–1 : 5,000,000") stimulated phagocytosis by horse leucocytes. Our experimental design is broadly similar to that of Moudgil and his colleagues (1977) who also used casein as the chemotactic agent, but they reported inhibition by 1% halothane. The present study shows a significant increase in random migration through a millipore filter, not in response to chemotaxis. This is further evidence of the very real possibility that activity may be enhanced by moderate concentrations of anaesthetics.

At least one important *caveat* applies to the study of the effect of anaesthetics on chemotaxis. There are many known chemotactic agents which probably react with different receptor molecules on the surface of the neutrophil. It is not possible to extrapolate from experiments with casein and halothane to generalize about the effect of other chemotactic agents and other anaesthetic agents. Further work will be required to determine how far studies of halothane and casein are representative of other situations.

The lack of an observed effect of halothane on oxygen consumption cannot be explained by the inevitable loss of halothane during transfer of the suspension to the cuvette and the addition of the latex particles. Our experimental design allowed for these changes and gas chromatographic studies (kindly undertaken by Dr Michael Halsey) showed the final partial pressure of halothane to be at least 75% of that of the gas mixture. Thus, with a gas mixture of 3% halothane, the final partial pressure was equivalent to 2.25% halothane or three times the minimal alveolar concentration required for anaesthesia.

The general conclusion which we draw is that concentrations of halothane considerably greater than those required for anaesthesia have no appreciable effect *in vitro* on a wide range of functions of neutrophils related to defence against bacterial invasions. All samples were withdrawn from healthy subjects who were free from stress. These essentially negative results may be contrasted with the studies of Cullen, Hume and Chretien (1975) and Stanley and his colleagues (1976), in which neutrophils extracted from blood withdrawn from anaesthetized patients showed defective phagocytosis. It seems likely that volatile anaesthetic agents would be lost during the process of separation of the neutrophils and, furthermore, we have found no evidence for any effect of anaesthetics *in vitro*. We may therefore draw the conclusion that the defective phagocytosis reported by these workers was not a result of the presence of anaesthetics and perhaps reflected the stress of the operative procedure. Impairment of phagocytosis by neutrophils withdrawn from anaesthetized patients was reported as early as 1911, by Graham. The mechanism by which this occurs merits further study.

There is a striking contast between the effect of halothane on the motility of neutrophils and that of lymphocytes since Nunn, Sharp and Kimball (1970) found that exposure to medium equilibrated with 2% halothane caused an almost total cessation of movement of thymic and pulmonary lymphocytes in culture. The effect occurred within 5 min and was completely reversible on exposure to fresh medium which did not contain anaesthetics. The clinical relevance of this difference is not clear, but it is a striking example of the difference in the effect of anaesthetics on biological systems which appear to be superficially similar.

Note added in proof: Professor G. Vourc'h has kindly drawn our attention to the work of Mlle Tannières (*Anesth. Analg.* (*Paris*) (1972), **29**, 509; MD Thesis (1974), Paris). Her studies of random motility of neutrophils on glass showed motility reduced to 91.5% of control after *in vitro* equilibration with 2% halothane, 87.9% with 3% halothane and 35.2% with 4% halothane. Broadly similar results were obtained with other volatile inhalation anaesthetics at equipotent concentrations. These results accord with our own view that *in vitro* exposure of neutrophils to the concentrations of halothane commonly employed for anaesthesia do not cause any appreciable impairment of motility.

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L'HALOTHANE N'INHIBE PAS LA FONCTION NEUTROPHILE HUMAINE *IN VITRO*

RESUME

On a examiné divers indices de la fonction des neutrophiles provenant de volontaires normaux en bonne santé, après exposition à l'halothane *in vitro*. Les mouvements libres effectués au hasard sous verre n'ont pas été affectés, mais la migration au hasard à travers les filtres millipores a augmenté légèrement. Il n'y a eu aucun changement significatif dans la migration en réponse à la chimiotaxie de la caséine. La phagocytose, la dégranulation et la respiration non-mitochondriale plus forte associées à la phagocytose n'ont pas été affectées. L'apparence au microscope électronique 30 s après exposition aux particules de latex a été normale à tous points de vue.

HALOTHAN UNTERBINDET NICHT DIE MENSCHLICHE NEUTROPHILFUNKTION *IN VITRO*

ZUSAMMENFASSUNG

Verschiedene Anzeichen der Funktion Neutrophiler, entnommen aus normalen, gesunden Freiwilligen, wurden *in vitro* nach der Aussetzung auf Halothan untersucht. Die willkurliche freie Bewegung auf Glas blieb unbeeinflusst, aber die willkürliche Abscheidung durch Millipor–Filter wurde etwas erhoht. Als Reaktion auf Kasein–Chemotaxis gab es keine wesentliche Änderung der Abscheidung. Phagozytose, Entkornung und die verstärkte nicht-mitochondrische Respiration im Zusammenhang mit Phagozytose wurden nicht beeinflusst. Der Anblick im Elektronenmikroskop, 30 s nach der Aussetzung auf Latex–Partikel war in jeder Hinsicht normal.

EL HALOTANO NO INHIBE LA FUNCION NEUTROFILA EN EL SER HUMANO *IN VITRO*

SUMARIO

Se examinaron varios índices de la funcíon de los neutrófilos en voluntarios sanos y normales después de su exposición *in vitro* al halotano. El movimiento libre fortuito en vidrio no fue afectado, pero la migración accidental a través de filtros milipores aumentó ligeramente. No hubo ningún cambio significativo de la migración como respuesta a la quimicotaxis por caseina. No hubo ninguna alteración de la fagocitosis, ni de la desgranulación y respiración no-mitocondrial realizada asociada con fagocitosis. En todos respectos, fue normal la aparición de electrones microscópicos 30 s después de la exposición a las partículas de latex.

Br. J. Anaesth. (1979), **51**, 1109

RELATIONSHIP BETWEEN CEREBRAL BLOOD FLOW CHANGES AND CORTICAL EXTRACELLULAR FLUID pH DURING CEREBRAL METABOLIC DEPRESSION INDUCED BY ALTHESIN

D. G. McDowall, D. Heuser, Y. Okuda, G. M. Jones and A. Wadon

SUMMARY

Baboons anaesthetized with halothane and nitrous oxide in oxygen were given Althesin 0.05 ml kg^{-1} i.v. Cerebral blood flow (c.b.f.) was measured by an electromagnetic flowmeter and by xenon clearance whilst extracellular fluid (e.c.f.) pH of the parietal cortex was measured with a micro pH electrode. Carotid blood flow (carBF) began to decrease and carotid vascular resistance (carVR) to increase 2.0 s (SEM 0.3) after the slowing of the e.e.g. produced by Althesin, while e.c.f. pH began to change to alkaline 10.5 s (SEM 1.0) after the e.e.g. change. The first statistically significant increase in mean e.c.f. pH occurred 25 s after the Althesin-induced change in the e.e.g. The duration of the changes in carVR and e.c.f. pH were 7 and 5 min respectively. It is concluded that the change in e.c.f. pH cannot have initiated the increase in carVR which followed the cerebral metabolic depression produced by Althesin. The later alkaline shift in e.c.f. pH may, however, have maintained the increased carVR during the duration of cerebral metabolic depression produced by Althesin.

The extracellular fluid pH of brain tissue is considered to be important in cerebrovascular control (Lassen, 1974). Supporting evidence comes from many different experiments, for example from studies in which the brain surface is perfused with mock cerebrospinal fluid at varying values of pH (Wahl et al., 1970), from correlations between cerebral blood flow (c.b.f.) and the concentrations of brain tissue metabolites (Kennedy et al., 1975) and from direct measurements of extracellular fluid (e.c.f.) pH (Betz and Heuser, 1967).

One circumstance in which e.c.f. pH may operate is in adjusting cerebral perfusion to meet metabolic demands. An increase in cortical activity, through the mechanism of an increase in carbon dioxide production, leads to an acidotic shift in cortical e.c.f. pH, which dilates the resistance vessels and c.b.f. increases to meet the new metabolic requirement of the brain. The converse sequence of events is believed to occur in conditions when cortical metabolic activity is decreased.

Althesin is a rapidly acting i.v. anaesthetic agent, which consists of two steroids—alphaxalone and alphadolone—dissolved in saline, with an emulsifying agent, cremophor EL. There is a steroid content of 12 mg ml^{-1} (alphaxalone 9 mg ml^{-1} and alphadolone 3 mg ml^{-1}). Althesin produces major decreases in c.b.f. and cortical oxygen uptake within short periods of time (Pickerodt et al., 1972; Keaney et al., 1978). It seemed that this anaesthetic could be used to investigate the possible links between flow and metabolism and we report here results of measurements of c.b.f. and cortical e.c.f. pH during the action of Althesin.

METHODS

Four baboons (*Papius papio*) of either sex and of weights between 9.2 and 13.3 kg were premedicated with phencyclidine 0.5 mg kg^{-1} i.m. and, 1 h later, anaesthesia was induced with halothane in nitrous oxide in oxygen. A cuffed orotracheal tube was inserted after the administration of suxamethonium i.m. Anaesthesia was maintained with nitrous oxide in oxygen and 0.5–0.7% inspired halothane during controlled ventilation under neuromuscular blockade produced with pancuronium 1 mg half-hourly i.m. The tidal volume was adjusted to produce normocapnia. Rectal temperature was maintained at 37 °C, using a heating blanket.

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Surgical preparation

A catheter for the administration of Althesin was inserted in one femoral vein and advanced into the inferior vena cava. This was confirmed post-mortem. A second venous catheter was inserted for the administration of replacement fluids (Hartmann's solution 5 ml kg^{-1} h^{-1}). A catheter in the abdominal aorta allowed continuous measurement of arterial pressure (BP) and intermittent sampling of arterial blood for blood-gas analysis. End-tidal carbon dioxide was recorded continuously with an infra-red carbon dioxide analyser.

An incision was made behind the ramus of the mandible and the carotid bifurcation was identified. A catheter was inserted in the lingual artery and advanced until its tip lay at the junction with the carotid. Xenon-133 in saline was injected through this catheter for the measurement of c.b.f. All branches of the common carotid other than the internal were then double-ligated. A catheter-type electromagnetic flow probe (EMF) was placed around the common carotid artery which, since all other branches had been ligated, measured internal carotid blood flow (carBF).

On the same side, scalp and temporalis muscle were reflected and excised at the level of the zygomatic arch. A more limited reflection of scalp and temporalis muscle was effected on the opposite side. Four brass screws were then positioned in the skull to give bitemporal and frontoparietal e.e.g. recordings.

A 1.5-cm trephine opening was made on the side of the carotid dissection and the dura opened over the superior parietal cortex. The micro pH electrode (see below) was inserted 0.5–1.0 mm into the cortical tissue using a micro-manipulator. The reference electrode was placed on the cortical surface within 0.1–0.3 mm of the tip of the pH electrode or its insertion point. Over the same cerebral hemisphere a collimated scintillation counter was positioned to record the clearance of xenon-133 from brain tissue after its bolus injection into the carotid artery. C.b.f. was assessed using the initial method of analysis of the xenon clearance curve (Paulson et al., 1969).

pH measurements

Local extracellular H^+-activity was measured with a glass micro-electrode which was built using a modification of the technique described by Gebert (1972). Tubes of H^+-selective glass (Ti-glass, Ingold Comp., Frankfurt, Germany) were pulled to capillaries with tip diameters of 2–5 μm. These capillaries were fitted into tubes of lead glass so that the sensitive glass protruded beyond the tip of the sealing glass. By gently heating with a micro-forge and simultaneously applying pressure to the pH capillary, the two glasses were melted together and the free end formed a small glass bulb with a tip diameter between 15 and 40 μm. The electrode was filled with an appropriate buffer solution and a chlorinated silver wire was inserted as internal reference. The open end was sealed with wax or silicone.

As reference electrode, an Ag/AgCl electrode was used which dipped into a small capillary tube of tip diameter 2–5 μm filled with isotonic sodium chloride solution. This system gave nearly ideal Nernstian potentials, which were recorded across the differential input of a d.c.-amplifier with high-input impedance ($> 10^{13}\ \Omega$). Calibration was performed with appropriate buffer solutions (Maas, 1971). The time constants (τ, 2τ, 3τ) of the system were 0.36 s, 0.63 s and 0.84 s during dynamic calibration (Heuser, 1977).

Experimental programme

No measurements were made for at least 1 h after opening the dura. Then a series of injections of Althesin 0.05 ml kg^{-1} or vehicle (same volume) was given into the central venous catheter. The term "vehicle" is used for the solvent in which the Althesin is normally supplied, and which consists of saline with cremophor as the emulsifying agent. Injections of Althesin were separated by at least 30 min.

Before each injection, control measurements of carBF, cortical e.c.f. pH and e.e.g. were made. Arterial pH, P_{CO_2} and P_{O_2} were measured before most injections and end-tidal P_{CO_2} was recorded before every injection. For 10 s before to 10 min after each injection carBF, cortical pH, e.e.g. and BP were recorded continuously. Carotid vascular resistance (carVR) was calculated as mean BP divided by mean carBF.

Since this study was concerned with the *timing* of changes in c.b.f. in relation to cortical pH measurement, the emphasis will be on the e.m.f. measurements of internal carBF. However, to verify that the changes seen in carBF were indicators of changes in tissue perfusion, xenon c.b.f. measurements were made before and 3 min after seven of the Althesin injections, in the four experiments. The c.b.f. values were calculated from the initial slope and therefore refer mainly to grey matter flow.

RESULTS

Control values, that is values measured immediately before either Althesin or vehicle injection, of arterial Po_2, Pco_2, pH, haemoglobin mean BP, carBF and carVR are given in table I. The values given for the last three parameters in table I form the 100% values used in figures 1 and 2.

The injection of Althesin caused a 7% decrease in mean BP (at 8 s), a 22% decrease in carBF (at 35 s), a 36% increase in carVR (at 35 s), and a 7% decrease in H+-activity (at 3 min) (fig. 1). The alkaline shift in e.c.f. pH was significant between 30 s and 5 min following the change in e.e.g. induced by Althesin (table II). Zero time in figures 1, 3 and 4 was the time of the first depression detected in the e.e.g. This time was used, rather than the time of injection, to avoid scatter as a result of variations in the central venous to brain circulation time. In figure 2, zero time is the time of central venous injection, since no e.e.g. change was discernible after injection of the vehicle.

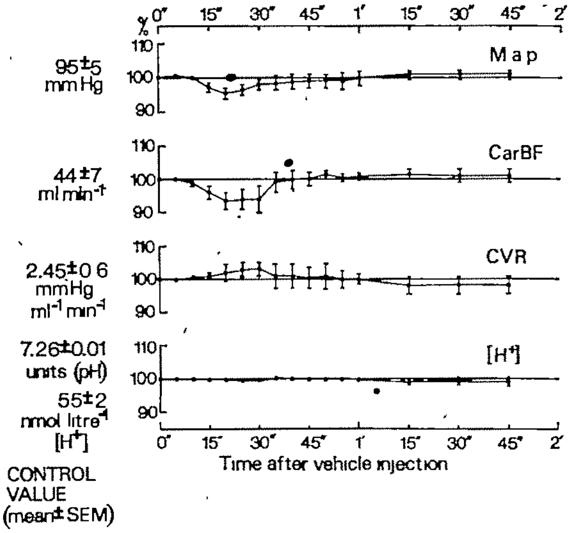

FIG. 1. Changes (%) in mean arterial pressure, carotid blood flow, carotid vascular resistance and H+-activity in relation to time following e.e.g. change induced by Althesin injection. The H+ measurements were made with the pH micro-electrode inserted 0.5–1 mm into the cortical mantle.

In order to time more precisely the changes in carVR and e.c.f. pH, produced by Althesin, all measurements have been plotted at 1-s intervals in figures 3 and 4. Following Althesin, there was an initial decrease in carVR, probably produced by the mild hypotension followed by a sharp increase (fig. 3). The time at which the initial trend of decreasing carVR was reversed by a trend of increasing carVR was at 2.0 s (SEM 0.3) after the e.e.g. change induced by Althesin. The first H+-activity value which was significantly different from control was that at the

TABLE I. *Control (pre-injection) values of arterial Po_2, Pco_2 and pH, haemoglobin, carotid blood flow, mean arterial pressure and carotid vascular resistance for both groups of e.c.f. pH measurements (mean values ± SEM). *In addition, end-tidal Pco_2 was measured throughout all experiments*

	Pa_{O_2} (kPa)	Pa_{CO_2}* (kPa)	pHa	Hb (g dl⁻¹)	Control stage CarBF (ml min⁻¹)	M.a.p. (mm Hg)	CVR (mm Hg ml⁻¹ min⁻¹)
Althesin ($n = 11$)	23.4 ± 1.5 $n = 7$	5.3 ± 0.3 $n = 8$	7.40 ± 0.02 $n = 7$	13.0 ± 0.6 $n = 5$	36 ± 9 $n = 11$	94 ± 9 $n = 11$	2.713 ± 0.671 $n = 11$
Vehicle ($n = 4$)	22.9 ± 0.1 $n = 3$	5.3 ± 0.1 $n = 3$	7.40 ± 0.01 $n = 3$	13.1 ± 1.2 $n = 2$	44 ± 13 $n = 4$	95 ± 11 $n = 4$	2.446 ± 1.210 $n = 4$

TABLE II. *Hydrogen ion activity (nmol litre⁻¹) (mean ± SD) measured in cortical tissue following Althesin 0.05 ml kg⁻¹ or vehicle (same volume) injection. Zero time for the measurements after Althesin is the time of first e.e.g. change, but for vehicle measurements is the time of central venous injection.* *$P < 0.05$

		Control	10 s	20 s	30 s	1 min	2 min	3 min	4 min	5 min	10 min
Althesin	Mean	49.81	49.81	49.11	48.51*	48.60*	46.62*	46.13*	46.73*	47.36*	47.85
	SD	5.28	5.08	4.81	4.69	5.08	5.37	5.39	5.59	6.04	7.13
	n	11	11	11	11	10	10	10	10	10	10
Vehicle	Mean	55.04	55.04	54.79	54.75	54.79	54.41	—	—	—	—
	SD	3.50	3.50	3.97	4.04	3.97	3.41	—	—	—	—
	n	4	4	4	4	4	4	—	—	—	—

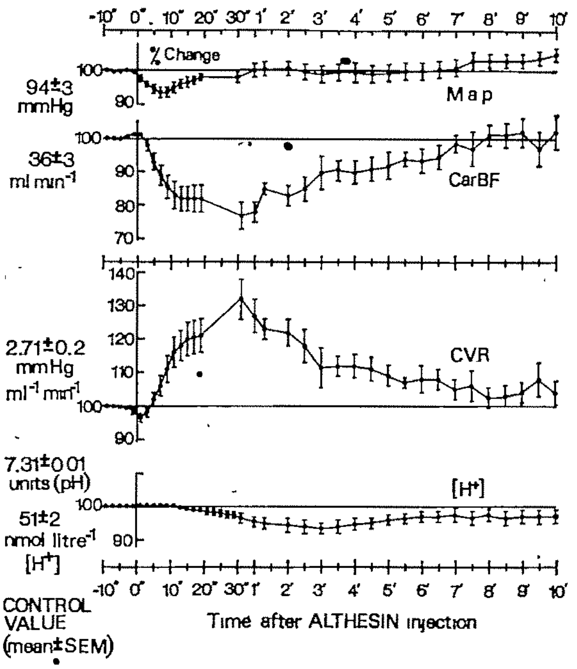

FIG. 2. Changes (%) in mean arterial pressure, carotid blood flow, carotid vascular resistance and H^+-activity following i.v. injection of the vehicle without Althesin.

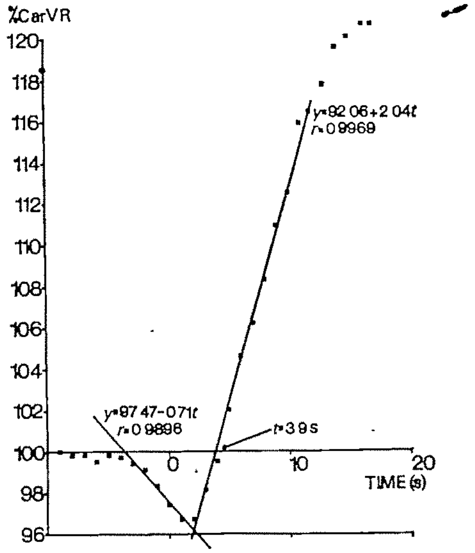

FIG. 3. Changes (%) in carotid vascular resistance following Althesin injection, zero time being the time of e.e.g. change. The initial decrease in carotid vascular resistance may be a result of the decrease in arterial pressure, while the subsequent increase in resistance is believed to be secondary to cerebral metabolic depression produced by the drug.

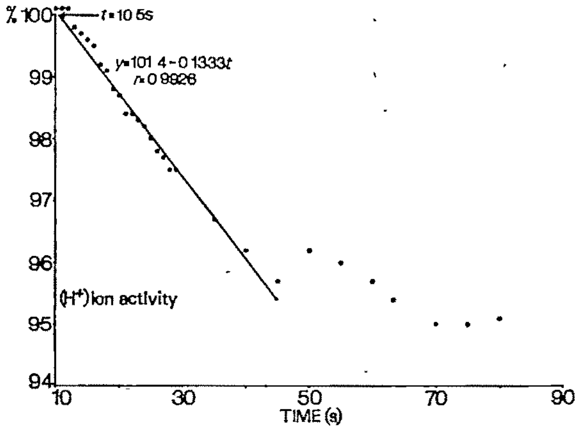

FIG. 4. Changes (%) in H^+-activity following Althesin injection. The regression line is fitted to the data points between 15 and 45 s following Althesin-induced e.e.g. depression. The point at which H^+-activity began to decrease was 10.5 s (SEM 1.0) after slowing of the e.e.g.

25th second after e.e.g. change. Inspection of figure 4 will show that, once H^+-activity began to decrease, it did so in a linear manner between approximately 10 s and 45 s. In order to determine the starting point of this trend a regression line has been fitted to the H^+-activity values between these times and extrapolated to the x axis ($y = 101.4 - 0.1333t$; $r = -0.9926$). Assessed in this way, H^+-activity began to decrease 10.5 s (SEM 1.0) after the first change in e.e.g. induced by Althesin. As regards the duration of the changes produced by Althesin, carVR and H^+-activity were no longer significantly

TABLE III. *C.b.f. (Fi) measured by xenon clearance, before and 3 min after Althesin injection*

	Control		3 min after Althesin	
Expt no.	*Fi* (ml min⁻¹/100 g)	Pa_{CO_2} (kPa)	*Fi* (ml min⁻¹/100 g)	Pa_{CO_2} (kPa)
192	98	6.3	31	6.3
	60	5.2	21	5.3
193	56	5.3	34	6.3
	55	5.5	31	6.4
	66	5.1	34	5.2
194	62	5.5	33	5.3
	38	5.2	29	5.3
195	38	5.3	29	5.3
	41	5.3	24	5.3
Mean	57.1	5.4	29.6	5.6
SD	±18.6	0.4	±4.5	0.5

different from control 7 min and 5 min after the change in e.e.g. respectively.

Xenon clearance measurements of c.b.f. showed a 52% decrease in c.b.f. (initial) 3 min following the injection of Althesin (table III).

DISCUSSION

In this study, c.b.f. has been measured by two techniques: (i) xenon clearance, and (ii) e.m.f. probe on the common carotid artery after ligation of the external branches. Both these techniques are valid measurements of c.b.f. in the baboon which, like man, possesses an internal carotid artery carrying blood predominantly to the brain. In this respect primates differ from most other species, in which the internal carotid artery is small and carries blood to extracranial tissues as well as to brain.

These techniques, however, measure flow in large regions of brain, whereas the pH micro-electrode is influenced only by H+-activity in its immediate vicinity (1–3 mm). Consequently, the pH readings may not have been representative of the wider area from which c.b.f. was measured. This seems unlikely, however, since the pH measurements were made in many sites selected at random on the parietal cortical surface. At every site, e.c.f. pH changed toward alkaline with the injection of Althesin. Furthermore, Rasmussen, Rosendal and Overgaard (1975) have shown that regional cerebral blood flow (rc.b.f.) decreases equally with Althesin in normal man in all regions of brain examined.

The presence of the electrode in the tissue may, however, have altered the local response of the c.b.f. to Althesin. Without measuring c.b.f. in precisely the same micro area as that from which pH measurement was obtained, it is impossible to discount this suggestion. Indeed, the work of Rasmussen, Rosendal and Overgaard (1975) has demonstrated that, in abnormal areas of brain, Althesin may increase local c.b.f., an effect which, through the wash-out of tissue carbon dioxide, would lead to an alkaline shift in e.c.f. pH. Against this possibility, however, are the values obtained for e.c.f. pH, which were within the normal range (mean measured e.c.f. pH = 7.305 ± 0.014), and did not suggest local acidosis from tissue damage. Furthermore, in one experiment it was shown that bicarbonate injected i.v. did not cross the blood–brain barrier at the site of the pH measurements. Experiments by Heuser and colleagues (1975) have confirmed that the blood–brain barrier to bicarbonate is preserved following placement of the H+ electrode. This maintenance of blood–brain barrier function argues against significant tissue damage produced by the pH electrode.

The present results confirm our earlier finding of a rapid major increase in carVR occurring about 2 s after Althesin-induced depression of the e.e.g. (Keaney et al., 1978). The tissue e.c.f. pH measurements showed a change in pH in the correct (alkaline) direction to explain the observed increase in carVR, but this occurred too late to account for the initiation of the change in carVR (i.e. carVR increase began at 2.0 s (SEM 0.3) after e.e.g. depression, while H+-activity began to decrease at 10.5 s (SEM 1.0) after e.e.g. change). The observed delay could not be the result of the response time of the H+ electrode, which is less than 1 s; nor could it be the result of the diffusion time of carbon dioxide to the pH-sensitive glass, since a change in blood $P\text{CO}_2$ is detected by the electrode within 5 s. By exclusion, therefore, the likelihood is that the carVR change is not initiated by the pH change, and this conclusion is in accord with the timing experiments of Keaney and colleagues (1978), from which it was calculated that the maximum change of tissue $P\text{CO}_2$ at the time of the initiation of the increase in carVR could not have been greater than 0.5 mm Hg.

Although the change in carVR does not appear to have been initiated by the change in e.c.f. pH, it may have been maintained by it, for a significant alkaline shift existed between 25 s and 5 min after depression of the e.e.g. by Althesin. We suggest that the increase in carVR was initiated by some fast-responding mechanism and maintained by the slower H+-activity change.

From the present measurements it is not possible to state what the initiating mechanism would be. Two obvious suggestions are that a neurogenic control mechanism is involved, or that the changes result from reductions in extracellular fluid potassium concentration. If the mechanism is neurogenic, then the pathway cannot involve the cervical sympathetic nervous system, since in earlier experiments Keaney and colleagues (1978) showed that section of the cervical sympathetic chain did not alter the time course of the carVR changes following Althesin. A mechanism involving the central sympathetic system originating from the locus coeruleus (Owman and Edvinsson, 1978) or the removal of tonic activity in a vasodilator pathway (Ponte and Purves, 1974) cannot be excluded. We believe, however, that a more likely initiating mechanism would be a sudden decrease in e.c.f. potassium ion concentration secondary to reduced neuronal activity. The situation would then be a mirror image of that proposed to account for the increase in c.b.f. accompanying seizure activity with increased e.c.f. potassium concentrations (Astrup et al., 1978).

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RELATION EXISTANT ENTRE LES VARIATIONS DU DEBIT SANGUIN CEREBRAL ET LE pH DU FLUIDE EXTRACELLULAIRE CORTICAL PENDANT UNE DEPRESSION METABOLIQUE CEREBRALE PROVOQUEE PAR L'ALTHESINE

RESUME

On a administré par voie intraveineuse de l'Althésine, à raison de 0,05 ml kg^{-1}, à des babouins anesthésiés à l'halothane et au protoxyde d'azote/oxygène. On a mesuré le débit sanguin cérébral (c.b.f.) à l'aide d'un débitmètre électromagnétique et d'un xénodiagnostic (recherche du vecteur responsable) pendant que l'on mesurait à l'aide d'une micro-électrode de pH, le pH du fluide extracellulaire (e.c.f.) du cortex pariétal. Le débit sanguin de la carotide (carBF) a commencé à diminuer et la résistance vasculaire de la carotide (carVR) à augmenter: 2 s (écart type des moyennes 0,3) après le ralentissement du e.e.g. causé par l'Althésine, alors que le pH du e.c.f. a commencé à virer à l'alcalinité 10,5 s (écart type des moyennes 1,0) après la variation de l'e.e.g. La première augmentation significative du point de vue statistique du pH de l'e.c.f. s'est produite 25 s après le changement dans l'e.e.g. provoqué par l'Althésine. La durée des variations dans la carVR et le pH de l'e.c.f. ont respectivement été de 7 et de 5 min. On en a conclu que la variation dans le pH de l'e.c.f. ne peut pas avoir déclenché l'augmentation de la carVR qui a suivi la dépression métabolique cérébrale produite par l'Althésine. Le déplacement alcalin ultérieur du pH de l'e.c.f. peut toutefois avoir maintenu l'augmentation de la carVR pendant la durée de la dépression métabolique cérébrale causée par l'Althésine.

VERHÄLTNIS ZWISCHEN ÄNDERUNGEN DES ZEREBRALEN BLUTFLUSSES UND DEM pH VON KORTIKALER EXTRAZELLULARER FLÜSSIGKEIT WÄHREND ZEREBRALER METABOLISCHER DEPRESSION DURCH ALTHESIN

ZUSAMMENFASSUNG

Mit Halothan und Stickoxyd in Sauerstoff narkotisierte Paviane erhielten 0,05 ml kg^{-1} Althesin intravenös. Der zerebrale Blutfluss (c.b.f.) wurde mit elektromagnetischem Durchflussmesser und mit Xenon-Ausscheidung gemessen, während die extrazelluläre Flüssigkeit (e.c.f.)/pH des Scheitelcortex mit einer pH-Mikroelektrode gemessen wurde. Der Carotis-Blutfluss (carBF) begann zu sinken und der Carotis-Gefässwiderstand (carVR) zu steigen 2,0 s (SEM 0,3), nachdem das Althesin eine Verlangsamung von e.e.g. bewirkt hatte, während e.c.f. pH 10,5 s

(SEM 1,0) nach der e.e.g.-Veränderung zu Alkalin umgewandelt zu werden begann. Der erste statistisch wesentliche Anstieg in mittlerem e.c.f. pH erfolgte 25 s nach der durch Althesin bewirkten Änderung von e.e.g. Die Dauer der Änderungen von carVR und e.c.f. pH betrug 7 bezw. 5 Minuten. Es wird geschlossen, dass die Änderung von e.c.f. pH nicht den Anstieg von carVR eingeleitet haben kann, der auf die durch Althesin hervorgerufene zerebrale metabolische Depression folgte. Die alkalische Verschiebung in e.c.f. pH könnte jedoch die erhohte carVR aufrescht erhalten haben, zu der es während der Dauer der zerebralen metabolischen Depression durch Althesin gekommen war.

RELACION ENTRE LAS ALTERACIONES DEL FLUJO SANGUINEO CEREBRAL Y DEL pH DEL FLUIDO EXTRACELULAR CORTICAL DURANTE UNA DEPRESION METABOLICA INDUCIDA POR ALTESINA

SUMARIO

Se administró 0,05 ml kg^{-1} de Altesina i.v. a unos mandriles anestesiados con halotano y óxido nitroso en oxígeno. Se midió el flujo sanguíneo cerebral (f.s.c.) por medio de un flujómetro electromagnético y por depuración con xenón, mientras se medía el pH del fluido extracelular (f.e.c.) de la corteza parietal por elétrodo micro-pH. El flujo sanguíneo de la carotida (FScar) empezó a disminuir y la resistencia vascular de la carotida (RVcar) a aumentar, 2,0 s (MES 0,3), después del aflojamiento del g.e.e. producido por la Altesina, mientras el pH del f.e.c. comenzaba a tornarse alcalino 10,5 s (MES 1,0) después del cambio del g.e.e. El primer aumento estadísticamente significativo en el pH medio del f.e.c. ocurrió 25 s después del cambio del g.e.e. inducido por Altesina. La duración de los cambios en la RVcar y el pH del f.e.c. fue de 7 y 5 min respectivamente. Se llega a la conclusión de que el cambio en el pH del f.e.c. no puede haber provocado el aumento de la RVcar siguió a la depresión metabólica cerebral producida por Altesina. Sin embargo, el viraje a alcálino del pH del f.e.c. puede haber sostenido el aumento de la RVcar durante el periodo de depresión metabólica cerebral producida por la Altesina.

Br. J. Anaesth. (1979), **51**, 1117

BRAIN WATER AND ELECTROLYTE DISTRIBUTION DURING THE INHALATION OF HALOTHANE

A. SCHETTINI AND W. W. FURNISS

SUMMARY

The brain concentrations of Na^+, K^+ and Cl^-, water content and total brain osmolality were measured in six normocapnic dogs under pentobarbitone narcosis (30 mg kg^{-1}). These studies were repeated in six additional dogs after exposure for 1 h to the inhalation of halothane 1% (end-tidal); there was an increase ($P < 0.05$) in Na^+, Cl^- and water content but no change in K^+ content in the grey matter, but in the white matter only Cl^- increased ($P < 0.05$). These findings were associated with a decrease in total brain osmolality ($P < 0.05$) and a negative brain–cisternal c.s.f. osmotic gradient. The changes in the grey cortical matter were interpreted as a pattern of metabolic brain oedema related to interference with water–ion transport mechanisms across cell membranes. The observed brain–c.s.f. osmolality deficit could be related to a time-lag in the intracellular water–solute adjustment or to a deficit in osmotically active brain amino acids induced by the anaesthetic agent, or both.

Disturbance in the regulation of brain water balance is a serious complication in c.n.s. disease and may result from an abnormality in the autoregulatory mechanism of the cerebral circulation or an abnormality of brain ionic homeostasis, or both. The administration of halogenated volatile anaesthetics in these circumstances may enhance the oedema in two ways: by increasing cerebral blood flow and hence intracranial volume via cerebral vasodilatation, and by altering directly c.n.s. water and electrolyte metabolism.

To verify this hypothesis we chose to study brain water and electrolyte (Na^+, K^+ and Cl^-) distribution in the brain of normal dogs subjected to halothane anaesthesia. Although it is well established that halothane is a potent cerebral vasodilator (McDowall, 1967), its influence upon brain water and ion distribution has not been documented. In an earlier study we reported that clinical concentrations of halothane increased the electrical impedance (1 kHz) in the normal brain of dogs (Schettini and Moreshead, 1978). The size and ionic strength of brain extracellular space can be estimated by impedance (van Harreveld, 1966). Since water and ion shifts into the cell are the major contribution to the increase in brain impedance (Ranck, 1964) it was important to measure these in the brain during the inhalation of halothane in the experimental animal.

To measure brain water, ions (Na^+, K^+ and Cl^-) and total brain osmolality in this study, we utilized the techniques of Arieff (Arieff et al., 1972, 1973; Arieff and Guisado, 1976; Arieff, Guisado and Lazarowitz, 1977). Our data indicate that halothane 1% (end-tidal) causes a metabolic oedema in the cerebral cortex (Rapoport, 1976).

METHODS

Mongrel dogs (18–25 kg) of either sex were studied. The dogs were divided into two equal groups. Group I (control) was studied under pentobarbitone 30 mg kg^{-1} narcosis; Group II (halothane) was studied during a steady state of alveolar halothane 1% concentration. The sequence of experiments between group I and group II was randomized.

In group I dogs anaesthesia was induced with pentobarbitone i.v., the trachea was intubated and the lungs ventilated mechanically (Harvard Respirator) with an oxygen in air mixture. Ventilation was adjusted to maintain Pa_{CO_2} near normal (Pa_{CO_2} 4.72 kPa, SEM 0.15). Adequacy of ventilation was verified by monitoring alveolar carbon dioxide (infra-red analyser: LB2, Beckman) and by frequently measuring arterial blood-gas tensions and pH. Narcosis was maintained with pentobarbitone for a total dose not exceeding

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30 mg kg^{-1} (induction and maintenance) given over a 3-h period.

Anaesthesia was induced in group II with a small dose of pentobarbitone (90–120 mg) which was necessary for tracheal intubation and then the lungs were ventilated artificially as group I (Pa_{CO_2} 4.39 kPa, SEM 0.17) with an air in oxygen mixture plus halothane in oxygen vapour delivered through a calibrated vaporizer (Fluotec). Alveolar halothane concentration was monitored with an infra-red analyser (LB2, Beckman) calibrated with known volumes of halothane in air mixtures before each experiment. Also, in group II dogs, arterial pressure was maintained at the pre-halothane value (±10 mm Hg) by means of a phenylephrine microdrip infusion (10 µg ml^{-1}). When the alveolar halothane concentration stabilized at 1% (30 min) the halothane experiment was commenced.

To permit recording of intravascular pressures via strain gauges (Statham P23dB) and for blood and c.s.f. sampling, a femoral artery and the cisterna magna were cannulated in all dogs shortly after the institution of mechanical ventilation. All the dogs received an i.v. infusion of 0.9% sodium chloride given at 45 ml h^{-1}. Body temperature was maintained at 37±0.5 °C with a heat lamp.

The phases of the experiment for each dog included: (1) repeated measurements of arterial blood-gas tensions, pH, plasma and c.s.f. electrolytes (Na^+, K^+, Cl^-) and osmolality; (2) removal of brain and sampling procedures; (3) treatment of brain samples for determination of total brain osmolality, Na^+, K^+ and Cl^- for grey and white matter and brain water content according to the methods of Arieff and colleagues (1972, 1973); (4) programming of the data through a microprocessor (Altair 8080, Intel. Corp., Santa Clara, California 95051) to calculate dilution factor, brain water content equations and for the analyses of variance of all the data. The time from the induction of anaesthesia to the removal of the brain and sampling was the same (150 min) in both groups of dogs.

Na^+ and K^+ concentrations were measured by flame photometry (Instrumentation Laboratories, Lexington, Massachusetts); Cl^- concentration by potentiometric titration (Buchler–Cotlove chloridometer); osmolality by freezing point depression (Fiske Instruments, Uxbridge, Massachusetts) and arterial blood Po_2, Pco_2, pH and HCO_3^- with a microelectrode system (BMS3, Radiometer, Copenhagen) maintained at 37 °C.

The removal of the brain and the sampling procedure were undertaken as described by Arieff and colleagues (1972). The cranial vault was removed carefully with a trephine and rongeur, leaving the dura intact. Absorbable gelatin (Gelfoam) and bone wax were used to ensure haemostasis; a dural hook and scissors were used to raise and remove the dura mater. Then, in rapid sequence, the previously exposed carotid arteries were occluded with umbilical tapes and in less than 10 s a sample (5 g) of brain was removed with a spatula and placed in liquid nitrogen. The frozen sample was transferred to a small mortar and pulverized while under liquid nitrogen. Five samples each approximately 0.4 g were placed in boiling double-distilled water for 90 min; the freezing point depression was measured on 0.5 ml of the supernatant. Three additional samples were placed in empty tared pre-weighed bottles for the determination of the water content (Arieff et al., 1973). The remaining cerebral hemispheres were removed rapidly and placed on filter paper, where grey and white matter representative of brain cortex were separated by blunt dissection. Three samples of both grey and white matter (approximately 0.5 g) were placed in tared conical flasks and the net weight of the individual sample was determined to the nearest 0.1 mg. After oven drying at 105 °C for 48 h they were weighed again to determine the water content of the samples. Each sample was then extracted for 24 h in nitric acid 0.75 mol litre^{-1} and the concentrations of Na^+, K^+ and Cl^- were determined on the supernatant. In the final calculation an adjustment was made for the dilution factor (DF), expressed as:

$$\mathrm{DF} = \frac{\text{nitric acid added (ml)}}{\text{wet weight of tissue (g)}}$$

where wet weight = (weight of flask and tissue sample) − weight of flask. Brain tissue osmolality was calculated from the equation (Arieff et al., 1972):

$$\mathrm{Osm_t} = \mathrm{Osm_s}\left(\frac{\mathrm{H_2O_a}+\mathrm{H_2O_t}}{\mathrm{H_2O_t}}\right)$$

where $\mathrm{Osm_t}$ = tissue osmolality; $\mathrm{Osm_s}$ = supernatant osmolality; $\mathrm{H_2O_a}$ = water added; $\mathrm{H_2O_t}$ = tissue water. Determinations of tissue water and added water were calculated in the manner described by Arieff and co-workers (1972). An average of five brain tissue osmolality measurements could be obtained in brain tissue samples of four dogs, while only two measurements could be obtained in the other two dogs because of technical difficulties.

A microprocessor (Altair 8080) was programmed to calculate the dilution factor, brain water, electrolyte content equation and analyses of variance. Initially, we had considered the use of unmatched *t* tests for the analysis of our data. This technique of analysis was discarded because of the unequal number of observations per cell; and because repeated *t* tests would be required to compare the means across several factors. For these reasons, comparisons between group I (control) and group II (halothane) were made using an unweighted means analysis of variance according to the technique outlined by Winer (1971). Although the test allowed for the variation of replicate in each cell, it does not use each point as a datum point. The level of significance was 5%.

RESULTS

The values for arterial blood-gas tensions, pH; plasma, cisternal c.s.f. concentrations of Na^+, K^+ and Cl^- and osmolality are presented in table I. The differences between group I (control) and group II (halothane) are not significant. Although c.s.f. Na^+, K^+ and Cl^- decreased with halothane, c.s.f./plasma ratios for these ions were still within the normal range.

In table II, Na^+, K^+ and Cl^- concentrations and percentage of water for both grey and white matter in group I are compared with the values reported by other investigators for normal dogs and rabbits. We have included data for rabbit brain because the rabbit appears to have the same electrolyte concentration as the dog and because data on dog brain Cl^- are inadequate. Our measurements for group I (control) fall within the same range of values reported by other researchers as normal for dogs and rabbits. Exceptions must be made for the values of Pappius (1967) which are consistently greater (table II). Brain tissue osmolality in group I (control) was 306.4 ± 6.4 (mean ± SEM) m osmol kg^{-1} H_2O, which compares with a value of 305 ± 5.0 (mean ± SEM) m osmol. kg^{-1} H_2O, reported by Arieff and colleagues (1973) (table III).

In the cortical grey matter from the brains of group II dogs receiving halothane 1%, Na^+, Cl^- and water content increased significantly ($P<0.05$). The increase in the water content of the grey matter (table III) was used to estimate brain cortex water uptake (van Harreveld, 1966):

$$\frac{78.32-x}{100-x}=\frac{79.07}{100.00}$$

From this, a mean uptake of 3.7% water was computed. In the white matter only Cl^- increased significantly ($P<0.05$).

However, the osmolality measured for the whole brain decreased significantly ($P<0.05$) under halothane anaesthesia (table III).

A comparison of plasma, cisternal c.s.f. and brain osmolality shows that in group I (control) the brain/plasma and brain/c.s.f. osmotic gradients were +3.9 m osmol and +0.4 m osmol, respectively; in group II (halothane) these gradients were reversed: −31.4 m osmol and −33.6 m osmol, respectively (tables I, III).

DISCUSSION

In dogs subjected to the inhalation of halothane 1% (end-tidal) we found increases in water, Na^+ and Cl^- content in the grey matter and no significant change in K^+ content. In the white matter, only Cl^- content increased significantly ($P<0.05$). These findings existed in the presence of a significant ($P<0.05$) decrease in total brain osmolality.

TABLE I. *Arterial blood-gas tensions (kPa) and acid–base balance (mmol litre⁻¹), plasma and cisternal c.s.f. electrolytes (mmol litre⁻¹) and osmolality (OSM) (m osmol kg⁻¹) in group I (barbiturates) and group II (halothane) dogs. Six dogs in each group*

	Plasma							Cisternal c.s.f.				C.s.f./plasma ratio		
	OSM	Na^+	K^+	Cl^-	pHa	Pa_{CO_2}	HCO_3^-	OSM	Na^+	K^+	Cl^-	Na^+	K^+	Cl^-
Group I														
Mean	302.5	142.4	3.28	121.8	7.34	4.72	18.4	306.0	145.5	2.91	126.5	1.02	0.89	1.03
SD	4.5	6.3	0.54	15.6	0.04	0.53	1.8	2.1	1.5	0.05	2.0			
Group II														
Mean	303.5	146.6	3.46	120.7	7.33	4.39	17.3	305.7	135.0	2.70	123.1	0.92	0.78	1.02
SD	3.6	10.0	1.06	5.3	0.04	0.41	1.8	6.2	1.7	0.10	2.5			

TABLE II. *Water (g/100 g wet weight) and electrolyte († mmol/kg water; rest of table: mmol/kg wet weight) composition of the cortical grey and subcortical white matter of the dog brain: comparison of control measurements made during barbiturate narcosis. * Rabbits appear to have the same brain electrolyte concentration as dogs (Katzman and Pappius, 1973)*

	Grey matter					White matter				
	Na^+	K^+	Cl^-	Na/K ratio	% H_2O	Na^+	K^+	Cl^-	Na/K ratio	% H_2O
Arieff and others (1973); *n* = 10 dogs; mean ± SEM	66.9 ±1.6†	122.0 ±1.0†	44.8 ±1.0†	0.54	80.2 ±0.4	70.7 ±1.4†	117.0 ±2.0†	50.8 ±1.6†	0.61	69.1 ±0.6
Present study; *n* = 6 dogs; mean ± SEM	65.6 ±1.0†	119.0 ±2.0†	48.1 ±0.9†	0.55	78.3 ±0.4	76.4 ±2.0†	116.5 ±2.9†	56.4 ±1.7†	0.66	69.9 ±1.0
Eichelberger and Richter (1944); *n* = 12 dogs; mean ± SD	51.1 ±5.8	95.6 ±4.7	36.7 ±1.2	0.53	76.1 ±0.8	—	—	—	—	—
Pappius (1967); *n* = 15 dogs; mean ± SD	60 ±4	98 ±6	—	0.61	80.1	57.0 ±3	78.0 ±6.5	—	0.72	66.1
Present study; *n* = 6 dogs; mean ± SD	51.4 ±3.0	93.4 ±6.9	38.4 ±3.8	0.55	78.3 ±1.7	53.4 ±5.7	81.6 ±8.8	39.4 ±4.8	0.65	69.9 ±1.0
van Harreveld, Hooper and Cusik (1961); *n* = 10 rabbits*;										
Katzman and Pappius (1973); mean ± SD	54.4 ±5.8	92.8 ±3.8	37.5 ±2.4	0.58	79.9 ±1.0	53.9	87.5	—	0.62	68.2

TABLE III. *Water and electrolyte distribution of the cortical grey and subcortical white matter of dog brain during halothane anaesthesia. § Cortical grey matter: g/100 g wet weight; subcortical white matter: g/100 g water; † whole brain sample; ‡ osmolality for whole brain; * P < 0.05 difference from control*

	Na^+	K^+	Cl^-	Na^+	K^+	Cl^-				
	(mmol/kg wet weight)			(mmol/kg dry weight)			H_2O§	H_2O (g/100 g dry wt.)	H_2O (g/100 g frozen wt.)†	Osmolality‡ (mosmol/kg H_2O)
Cortical grey matter										
Control group										
n = 6 dogs										
Mean	51.37	93.36	38.45	237.51	435.86	175.43	78.32	361.96	75.55	306.4
SD	3.04	6.95	3.79	20.83	54.65	19.52	1.66	29.83	1.44	17.7
SEM	0.72	1.69	0.89	4.91	13.25	4.61	0.39	7.03	0.36	6.4
Halathone group										
n = 6 dogs										
Mean	54.21	94.87	42.42	258.92	454.67	201.56	79.07	378.54	75.47	272.1
SD	3.14	2.87	2.70	11.47	33.83	11.15	1.13	25.06	1.73	23.0
SEM	0.74*	0.68	0.64*	2.70*	7.97	2.63*	0.26*	5.90*	0.42	6.9*
Subcortical white matter										
Control group										
n = 6 dogs										
Mean	53.45	81.58	39.45	178.52	274.26	131.60	69.92	234.04		
SD	5.70	8.79	4.82	20.21	35.65	15.53	1.00	13.97		
SEM	1.34	2.13	1.11	4.76	8.65	3.66	0.23	3.29		
Halothane group										
n = 6 dogs										
Mean	57.87	84.32	43.80	194.43	287.24	147.53	70.16	237.08		
SD	4.19	4.95	2.68	14.92	31.53	14.58	1.88	22.58		
SEM	0.99	1.20	0.63*	3.52	7.65	3.44*	0.44	5.47		

Before determining that the above findings were the result of the inhalation of halothane, we must consider whether or not they may be attributable to technical artefacts. It may be argued first that we do not have a control group, but rather a comparison between measurements taken under pentobarbitone narcosis and under halothane anaesthesia. This appears semantic, since there is clear evidence that barbiturate narcosis does not affect water and ion distribution in the brain (van Harreveld, Hooper and Cusik, 1961; Chan and Quastel, 1970). These data exclude the possibility that the small induction dose (90–120 mg) of pentobarbitone used in the halothane group of dogs might have any residual effect at the time of sampling (150 min). One source of artefact could be that the difference between the control and halothane group may be a result of a different degree of cerebral trauma during craniotomy and brain sampling. Because barbiturates decrease cerebral blood flow and volume (Lassen and Tweed, 1975) and halothane has an opposite effect (McDowall, 1967), it may be argued that the oedema fluid in the halothane group derives from the circulating blood volume, or even indicates an increased quantity of blood contaminating the tissue samples. These artefacts, however, can be excluded because circulating blood which is low in K^+ would dilute brain tissue K^+, consequently decreasing the K^+ concentration of both grey and white matter. This is contrary to our findings, since brain K^+ concentration did not change (see table III).

Second, because plasma osmolality did not change during the inhalation of halothane, there would be no reason for a plasma–brain osmotic gradient. On the contrary, total brain osmolality decreased by 31 m osmol in the halothane group. A third potential artefact is that the increase in Na^+ and Cl^- content is only apparent and the result of a chemical analysis of solutes and water obtained from a tissue after it has been destroyed and may not accurately measure the concentration of the ions *in vivo* (there would be a tendency to overestimate Na^+ or K^+, or both, part of which had been bound by a tissue component destroyed during preliminary ashing). This hypothesis cannot stand since brain osmolality was decreased instead of being increased. For the above reasons, we believe that our findings represent a metabolic response of the dog brain to halothane inhalation. In this context, we shall consider first the changes in the grey matter, then Cl^- in the white matter and finally the apparent paradox of the decrease in brain osmolality.

Changes in the grey matter

An increase in Na^+ content of grey matter dry weight means that cerebral cortex has gained Na^+; Cl^- and water accompany the excess Na^+. This indicates also oedema of the cerebral cortex because the grey matter gained 3.7% water. These findings are analogous to those reported by Baetman and van Harreveld (1973) in rats and mice pretreated with 6-aminonicotinamide, a metabolic inhibitor. When these animals were sacrificed after pretreatment, the results showed an increase of 13% in the uptake of brain water and increases in Na^+ and Cl^- which were limited to the grey matter, while K^+ did not change. Swelling was restricted to the glial cells, which resulted in a moderate decrease in brain extracellular space. Another analogy to our findings in their studies is that the onset of brain oedema in their pretreated animals was presaged by a 25% increase in the low frequency (1 kHz) brain electrical impedance. Halothane invariably causes an increase, although of a lesser magnitude, in the low frequency (1 kHz) brain electrical impedance (Schettini and Moreshead, 1978).

Baetman and van Harreveld (1973) believed that 6-aminonicotinamide, by incorporating in NAD (nicotinamide adenine dinucleotide) or NADP (nicotinamide adenine dinucleotide phosphate), or both, blocked the oxidation of NADH or NADPH, or both. This inhibition interfered with the energy necessary for the Na/K pump, thus allowing Na^+, Cl^- and water to accumulate in the grey matter. Similarly, evidence from other laboratories suggests that clinical concentrations of halothane interfere with ion transport mechanisms across cell membranes (Ueda, 1965; Cohen and Marshall, 1968). In a recent monograph, Rapoport (1976) has categorized the oedema limited to the grey matter as metabolic oedema, in that the active ion transport mechanisms across cell membranes are inhibited, resulting in intracellular accumulation of Na^+ in excess of K^+ that is lost while Cl^- and water accompany the excess Na^+.

Based upon our studies and the supportive evidence listed above, we believe that halothane-induced oedema fits into this category of brain oedema, at least for alveolar concentrations of 1% or greater.

White matter Cl^-

The increase in Cl^- in the white matter cannot be readily explained. It could be that measured Cl^- is the halogen of a halothane metabolite or intermediary metabolite that has bound with intracellular phospholipids (Van Dyke and Wood, 1975). Alternatively, the increased Cl^- reflects an increase in member permeability or altered membrane transport for this anion, or both. It has been suggested (Katzman and Pappius, 1973) that Cl^- is transported actively in and out of c.n.s. cells by active mechanisms that are not linked to the Na/K pump.

Brain osmolality

The discrepancy between c.s.f. osmolality and brain osmolality deserves some comment. An artefactual decrease in osmotic activity, secondary to loss in molecular carbon dioxide or release of bound water, could have occurred when we boiled the frozen tissue sample before measuring the supernatant freezing point depression, but the losses in carbon dioxide or gain in water are far too small (Arieff et al., 1972) to account for our deficit. Furthermore, they were not seen in the control dogs (group I). In our opinion the c.s.f.–brain osmotic gradient may be explained in three ways.

(1) The brain is lagging behind in adjusting its intracellular osmolality in response to alteration in intracellular solutes and water. In rabbits subjected to acute hyperosmolality for 1 h, Arieff and co-workers (1972) observed that brain tissue osmolality lagged behind c.s.f. and plasma osmolality by 5 m osmol and 14 m osmol kg^{-1}, respectively. When the acute hyperosmolality was sustained for 4 h, the osmotic gradient disappeared. In our halothane group, however, the c.s.f.–brain osmotic gradient was considerably greater (33 m osmol).

(2) There may be a decrease in the availability of osmotically active intracellular cations, because of an increase in the binding of cations. It is believed that normally about 20% of intracellular Na^+ or K^+ or both is bound in the brain (Katzman and Pappius, 1973). Presumably, the surplus cations are bound to intracellular lipoproteins (Christensen and Hastings, 1940) and brain tissue macromolecules (Schettini and Moreshead, 1978). It has been proposed that, in hyper- and hypo-osmolality syndromes, a change in intracellular binding of Na^+ or K^+ influences the genesis of "idiogenic osmoles"* in the brain, which would account, at least in part, for the discrepancy between the net gain or loss of cellular solute and the expected change in brain tissue osmolality (McDowell, Wolf and Steer, 1955; Holliday, Kalayci and Harrah, 1968; Arieff, Guisado and Lazarowitz, 1977). An increase in the binding of cations in our experiments could have been secondary to conformational changes in brain tissue lipoproteins, as induced by the anaesthetic molecule (Eyring, Woodbury and D'Arrigo, 1973). A major objection to this hypothesis is that when brain tissue osmolality is extracted with boiling water (Appelboom et al., 1958), we would expect the bound cations to be released and osmotically active again upon boiling the frozen tissue sample. This did not happen.

(3) The brain failed to adjust its intracellular osmolality because of a deficit in intracellular free amino acids. In both vertebrates and invertebrates, Baxter and his colleagues (Baxter and Ortiz, 1966; Baxter, 1968; Shank and Baxter, 1973) have documented that brain tissue free amino acids (glutamine, glutamate, GABA, aspartate and alanine) and the specific activities of several related enzymes were sensitive to changes in the osmotic environment of the brain. In rats made hypernatraemic, Lockwood (1975) found that brain content of glutamine increased and accounted for 20% of the discrepancy between the sum of brain cations and expected brain volume.

With the inhalation of halothane, a decrease in intracellular osmotically active amino acids in the brain could have occurred, because either the rate of amino acid efflux was increased or the rate of synthesis was decreased, or both. An increase in the efflux rate could have been prompted by the intracellular accumulation of Na^+, because of ATPase inhibition (Hammerstad and Cutler, 1972). A decrease in the rate of synthesis could have occurred because either glucose flux through the carboxylic cycle was reduced or transamination was diminished, or both. Unfortunately, studies of free amino acids in brain tissue and of specific related enzyme activities during the inhalation of halothane are conflicting and incomplete (Amakata and Greene, 1969; Biebuyck and Hawkins, 1972; Biebuyck, Dedrick and Scherer, 1975; Cheng and Brunner, 1975; Hulands, Beard and Brammall, 1975).

In conclusion, the present results and impedance findings reported earlier (Schettini and Moreshead, 1978) indicate that the inhalation of alveolar halothane 1% causes metabolic brain oedema. However, the mechanism underlying brain tissue hypo-osmolality seen with halothane remains unclarified. It could be related to an unsteady state of distribution of intracellular water and solutes or a decreased availability of osmotically active amino acids, or both, in the brain.

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* Undetermined intracellular solute, which can be osmotically activated or inactivated, depending upon the experimental conditions (Arieff and Guisado, 1976).

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REPARTITION DE L'ELECTROLYTE ET DE L'EAU DU CERVEAU PENDANT L'INHALATION D'HALOTHANE

RESUME

Les concentrations de Na^+, de K^+ et de Cl^- dans le cerveau, ainsi que l'osmolalité totale du cerveau et sa teneur en eau ont été mesurées sur six chiens en état de normocapnie sous narcose au pentobarbitone ($30\ mg\ kg^{-1}$). Ces études ont été recommencées sur six autres chiens après que ceux-ci aient été exposés pendant une heure à l'inhalation d'halothane à 1% (fin du volume courant); il y a alors eu une augmentation ($P<0{,}05$) dans la teneur en en Na^+; Cl^- et en eau, mais aucun changement dans la teneur en K^+ de la matière grise; dans la matière blanche seul le Cl^- a augmenté ($P<0{,}05$). Ces constatations ont été associées à une diminution de l'osmolalité totale du cerveau ($P<0{,}05$) et à une pente osmotique négative du cerveau–liquide cérébrospinal de la citerne. Les changements qui se sont produits dans la matière corticale grise ont été interprétés comme étant un signe clinique caractéristique d'un œdème métabolique du cerveau relié à l'interférence avec les mécanismes de transport eau–ions à travers les membranes des cellules. Le déficit dans l'osmolalité cerveau–liquide cérébrospinal que l'on a constaté pourrait être relié à un décalage dans le temps de l'ajustement intracellulaire eau–corps en solution ou à un déficit en amino acides agissant par osmose sur le cerveau, créé par l'agent anesthésiant, ou encore par ces deux causes.

REGENWASSER UND ELECTROLYTISCHE VERTEILUNG WÄHREND DER INHALATION VON HALOTHAN

ZUSAMMENFASSUNG

Die Gehirnkonzentrationen von Na^+, K^+ und C^-, der Wassergehalt und die gesamte Gehirnosmolalität wurden bei sechs normokapnischen Hunden unter Pentobarbiton-Narkose ($30\ mg\ kg^{-1}$) gemessen. Diese Studien wurden bei sechs weiteren Hunden nach Aussetzung auf die Einatmung von 1% Halothan (Ausatmung) wiederholt; dabei gab es einen Anstieg ($P<0{,}05$) von Na^+, Cl^- und des Wassergehalts, doch keine Veränderung von K^+ in der grauen Substanz, doch allein in der weissen Substanz stieg Cl^- an ($P<0{,}05$). Diese Resultate wurden mit einem Sinken der gesamten Gehirnosmolalität ($P<0{,}05$) und mit einem negativen osmotischen Gefälle der zerebrospinalen Flüssigkeit in der Gehirnzisterne in Zusammenhang gebracht. Die Veränderungen in der grauen kortikalen Substanz wurden als Form eines metabolischen Gehirnödems aufgrund von Störungen der Wasserionenverbreitung durch die Zellmembranen interpretiert. Die beobachtete mangelnde Osmolalität von Gehirn und zerebrospinaler Flüssigheit wurde entweder auf eine verspätete Adjustierung der intrazellularen Wasserlöslichkeit oder auf den Mangel an osmotisch aktiven Gehirn-Aminosäuren aufgrund des Narkosemittels oder auf beides zurückgeführt.

DISTRIBUCION DEL AGUA CEREBRAL Y DEL ELECTROLITO DURANTE LA INHALACION DE HALOTANO

SUMARIO

Se midieron las concentraciones de Na^+, K^+ y Cl^-, del contenido de agua y de la osmolalidad cerebral total en el cerebro de seis perros normocápnicos sometidos a narcosis por pentobarbitona ($30\ mg\ kg^{-1}$). Se repitieron dichos estudios en seis perros adicionales, después de exponerlos durante 1 h a una inhalacion de halotano al 1% (extremo-respiratorio); hubo un aumento ($P<0{,}05$) del Na^+, Cl^- y del contenido de agua, pero ninguna alteración del contenido de K^+ en la materia gris, mientras, en la materia blanca, aumentaba únicamente el Cl^- ($P<0{,}05$). Se atribuyó esos resultados a una disminución de la osmolalidad cerebral total ($P<0{,}05$) y a un gradiente osmótico negativo cerebral–f.c.e. de los espacios cerebrales. Se interpretó a las alteraciones de la materia cortical gris como siendo una manifestación de un edema cerebral metabólico relacionado con interferencias en los mecanismos de traslado de los iones–agua a través de las membranas de las células. El déficit de osmolalidad f.c.e.–cerebral observado podría relacionarse con un retardo en el ajuste de la solución acuosa intracelular o con un déficit de aminoácidos cerebrales osmóticamente activos inducido por el agente anestético, o con ambos.

Br. J. Anaesth. (1979), 51, 1125

METHODOLOGY OF A PROSPECTIVE STUDY OF CHANGES IN LIVER ENZYME CONCENTRATIONS FOLLOWING REPEAT ANAESTHETICS

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SUMMARY

The methodology of a large prospective study on the influence of repeated anaesthetics on liver function is reported and the problems involved are discussed. The most suitable patients were those presenting for endoscopic examination of the bladder and urethra, for urethral dilatation and for cervical implantation of radium. Blood samples were taken immediately before induction of anaesthesia and on days 3–4 and 13–15 after operation, when a clinical assessment of the patient was also carried out. The concentrations of six enzymes (lactate dehydrogenase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, serum cholinesterase and gamma glutamyl transpeptidase) were chosen specifically as indices of liver function. The eosinophil count was measured to reflect any hypersensitivity reaction. The non-Gaussian distribution of these necessitated using appropriate non-parametric tests together with parametric tests on logarithmic transformed data. In addition a quantal method was used to measure the frequency of patients showing an "abnormal" increase in enzyme concentrations.

Unexplained hepatitis in some patients following halothane anaesthesia resulted in the setting up of the National Halothane Study in the United States in 1963. This retrospective survey of more than 850 000 anaesthetics implicated halothane as a cause of massive hepatic necrosis in less than 1 in 10 000 administrations (Bunker et al., 1969). Subsequently, various workers (Mushin, Rosen and Jones, 1971; Sharpstone, Medley and Williams, 1971; Inman and Mushin, 1974) incriminated repeated exposure to halothane and reported that there was an increase in the likelihood of liver dysfunction as the interval between successive halothane anaesthetics decreased.

"Halothane hepatitis" is characterized by the appearance of fever up to 2 weeks after anaesthesia, followed by symptoms resembling viral hepatitis. Often eosinophilia is found, which is in keeping with the view that the liver damage may be the result of a delayed hypersensitivity response to halothane or one of its metabolites (Moult and Sherlock, 1975; Walton et al., 1976).

However, controversy continues about a direct relationship between halothane and liver damage after operation as it has not been shown conclusively that halothane is implicated to a greater extent than any other anaesthetic agent (Simpson, Strunin and Walton, 1973; Conn, 1974; Dykes, 1977).

In 1975 the Medical Research Council set up a working party on "The effect of repeated exposure to anaesthetics" and later expressed willingness to finance studies on the influence of repeated anaesthetics on liver function. They supported partially a large prospective study, organized in Belfast. This paper reports on the methodology of this study, which has been in progress since early 1976, and discusses the problems involved and the solutions which have been suggested. The selection of suitable patients, the choice of anaesthetic technique, the biochemical monitoring of liver function and the recording of data and its analysis are discussed. In addition, the staffing of the study and the costs involved are worthy of note. Although there is some overlap between these various points, each will be considered separately.

OBJECTIVES

The study was concerned with the total effects of the anaesthetic agents and surgical procedures on the patients as reflected by morbidity and mortality during and after operation. In addition to clinical assessment it involved biochemical monitoring to

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detect any deleterious effects on hepatic function. It was hoped that the data obtained would allow a comparison between halothane and other agents, with particular reference to the problems of repeated exposure.

The study was designed to answer the following questions:

(1) What is the extent of the relationship between the repeated administration of halothane and other anaesthetic agents and the subsequent development of liver dysfunction?

(2) What groups of patients are especially liable to develop liver damage after halothane anaesthesia?

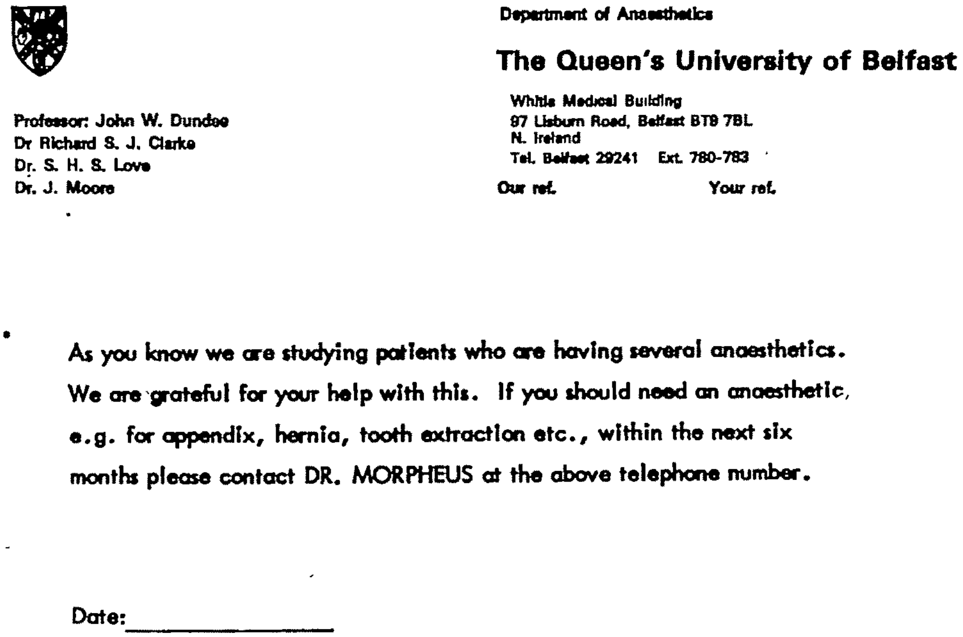
(3) How does the safety of repeated anaesthesia with halothane compare with that of other anaesthetic agents?

In the initial programme the other agents to be considered included trichloroethylene and methoxyflurane, but the use of these has diminished markedly with the availability of enflurane which became eventually the main alternative aneasthetic agent.

CHOICE OF PATIENTS

The greatest problem was obtaining access to a distinct, easily identified group of patients who have a reasonable chance of receiving another anaesthetic within a period of less than 6 months. They must be relatively free from sepsis and not receiving therapy which would adversely affect liver function. The operation must not be major abdominal or thoracic and blood transfusion must not be necessary; one must be able to vary the form of anaesthetic safely at will. Initially it was thought that patients presenting for minor urological procedures, burns and plastic surgery and orthopaedic operations would be particularly suitable. In practice, however, the last two groups were not available in sufficient numbers and the study eventually centred on patients presenting for endoscopic examination of the bladder and urethra, for urethral dilatation and for cervical implantation of radium. These include a large proportion of outpatients which made time-consuming domiciliary visits necessary and required a greater degree of patient co-operation than with inpatients. In addition there was less opportunity for clinical assessment of the patient than had been hoped for originally.

Organization of this study required very close co-operation with surgical and other colleagues. Hospital lists had to be scrutinized for suitable patients and the necessary arrangements made. Each patient was given an explanatory letter with a contact telephone number (fig. 1), and a card setting out details of the expected home visits.



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Our ref. Your ref.

As you know we are studying patients who are having several anaesthetics. We are grateful for your help with this. If you should need an anaesthetic, e.g. for appendix, hernia, tooth extraction etc., within the next six months please contact DR. MORPHEUS at the above telephone number.

Date:________________

FIG. 1. Explanatory letter to patients.

Even with this selection it was found that a high percentage of patients admitted did not have a repeat anaesthetic within 6 months. In 1977, 103 new patients were admitted to the study, of which 57 had no repeat anaesthetic within 6 months. During this period a total of 760 biochemical and clinical assessments were made. Some patients who had a further anaesthetic at another hospital, unknown to the study team, were lost from the study. Others changed address, went on holiday or had returned to work after the operation and so were unable to be seen on the required days after operation. Two patients died, although this was not associated with their operations and neither had a repeat anaesthetic.

A decision was taken not to include any new patients when the study had been fully established for a period of 2 years. Those patients presenting for repeat anaesthetics only were followed for a further 6 months. The total number of patients having one or more of the two anaesthetic agents is given in table I.

TABLE I. *Total numbers of patients having one or more of the two principal anaesthetic agents*

Halothane administrations	*n*	Enflurane administrations	*n*
1	143	1	152
2	70	2	69
3	23	3	26
4	10	4	10
5	4	5	4
6	1	6	—

ALLOCATION OF PATIENTS

The study started initially with halothane and over the 1st year all new patients were given this as their first anaesthetic. It was proposed to follow four sequences for patients having repeat anaesthetics (H = halothane; E = enflurane):

	1	2	3	4
Sequence A	H	H	H	H
Sequence B	H	H	E	E
Sequence C	E	E	E	E
Sequence D	E	E	H	H

In practice, the shortage of patients having up to four anaesthetics limited the study to the first three sequences. Also included are a number of patients who had an exposure to halothane (H) in the 6 months before admission to the study. These gave the following additional groups:

		1	2	3
Sequence E	(H)	H	H	H
Sequence F	(H)	H	H	E
Sequence G	(H)	H	E	E
Sequence H	(H)	E	E	E

ANAESTHESIA

Patients presenting for anaesthesia were premedicated, at the discretion of the anaesthetist, with atropine, diazepam or pethidine, alone or in combination.

Before induction, heart rate and arterial pressure were measured. Anaesthesia, induced with sodium thiopentone 4–5 mg kg^{-1}, was maintained with nitrous oxide 6 litre min^{-1} in oxygen 3 litre min^{-1} plus either halothane or enflurane as required. A semi-closed circuit with face mask was used in all patients, with a separate anaesthetic machine and tubing being used for each agent.

Following the anaesthetic, patients were taken to the recovery ward and, if outpatients, accompanied home later the same day.

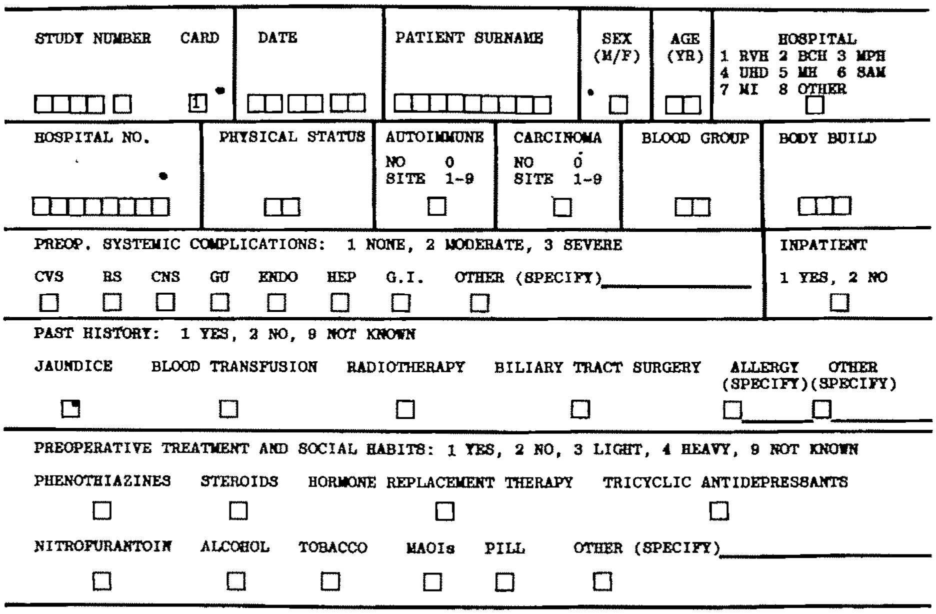
RECORDING OF DATA

Information was obtained relating to the patient's age, sex, A.S.A. grading of physical status, weight and body build. Past medical and surgical history and any recent or present drug therapy were noted also. Any complication before operation was assessed as mild, moderate or severe, depending on its effect on the system involved. The main intraoperative agent and any premedication, supplementary anaesthetic agent or neuromuscular blocking drugs used were recorded, as were details of any i.v. fluid therapy.

The site of surgery and the total anaesthetic time were noted. Any intraoperative anaesthetic complications were assessed as having a mild, moderate or severe effect on the system involved and the patient's condition on leaving the operating theatre was noted. The findings were recorded on four computer-compatible charts, one of which is shown in figure 2. The chart relating to the complications and condition of the patients after operation is shown in figure 3.

BIOCHEMICAL MONITORING OF LIVER FUNCTION

The problems which arose here concerned which tests to carry out and the time of blood sampling in relation to anaesthesia. With regard to the former, a serum "block analysis" was available at the Department of Biochemistry, the Royal Victoria Hospital, Belfast,



STUDY NUMBER ☐☐☐☐ ☐	CARD 1	DATE ☐☐☐☐☐☐	PATIENT SURNAME ☐☐☐☐☐☐☐☐☐☐	SEX (M/F) ☐	AGE (YR) ☐☐	HOSPITAL 1 RVH 2 BCH 3 MPH 4 UHD 5 MH 6 SAM 7 MI 8 OTHER ☐

HOSPITAL NO. ☐☐☐☐☐☐☐☐	PHYSICAL STATUS ☐☐	AUTOIMMUNE NO 0 SITE 1-9 ☐	CARCINOMA NO 0 SITE 1-9 ☐	BLOOD GROUP ☐☐	BODY BUILD ☐☐☐

PREOP. SYSTEMIC COMPLICATIONS: 1 NONE, 2 MODERATE, 3 SEVERE

CVS	RS	CNS	GU	ENDO	HEP	G.I.	OTHER (SPECIFY)________
☐	☐	☐	☐	☐	☐	☐	☐

INPATIENT
1 YES, 2 NO
☐

PAST HISTORY: 1 YES, 2 NO, 9 NOT KNOWN

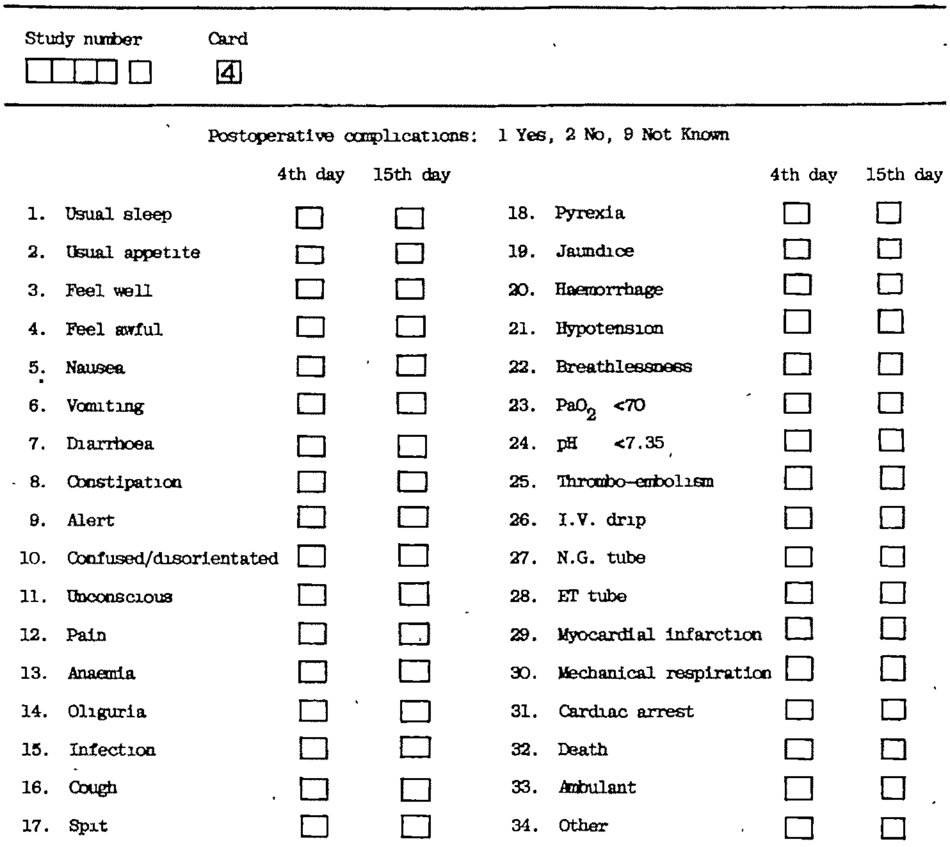
JAUNDICE	BLOOD TRANSFUSION	RADIOTHERAPY	BILIARY TRACT SURGERY	ALLERGY (SPECIFY)	OTHER (SPECIFY)
☐	☐	☐	☐	☐________	☐________

PREOPERATIVE TREATMENT AND SOCIAL HABITS: 1 YES, 2 NO, 3 LIGHT, 4 HEAVY, 9 NOT KNOWN

PHENOTHIAZINES	STEROIDS	HORMONE REPLACEMENT THERAPY	TRICYCLIC ANTIDEPRESSANTS
☐	☐	☐	☐

NITROFURANTOIN	ALCOHOL	TOBACCO	MAOIs	PILL	OTHER (SPECIFY)________
☐	☐	☐	☐	☐	☐

FIG. 2. Computer-compatible patient chart.

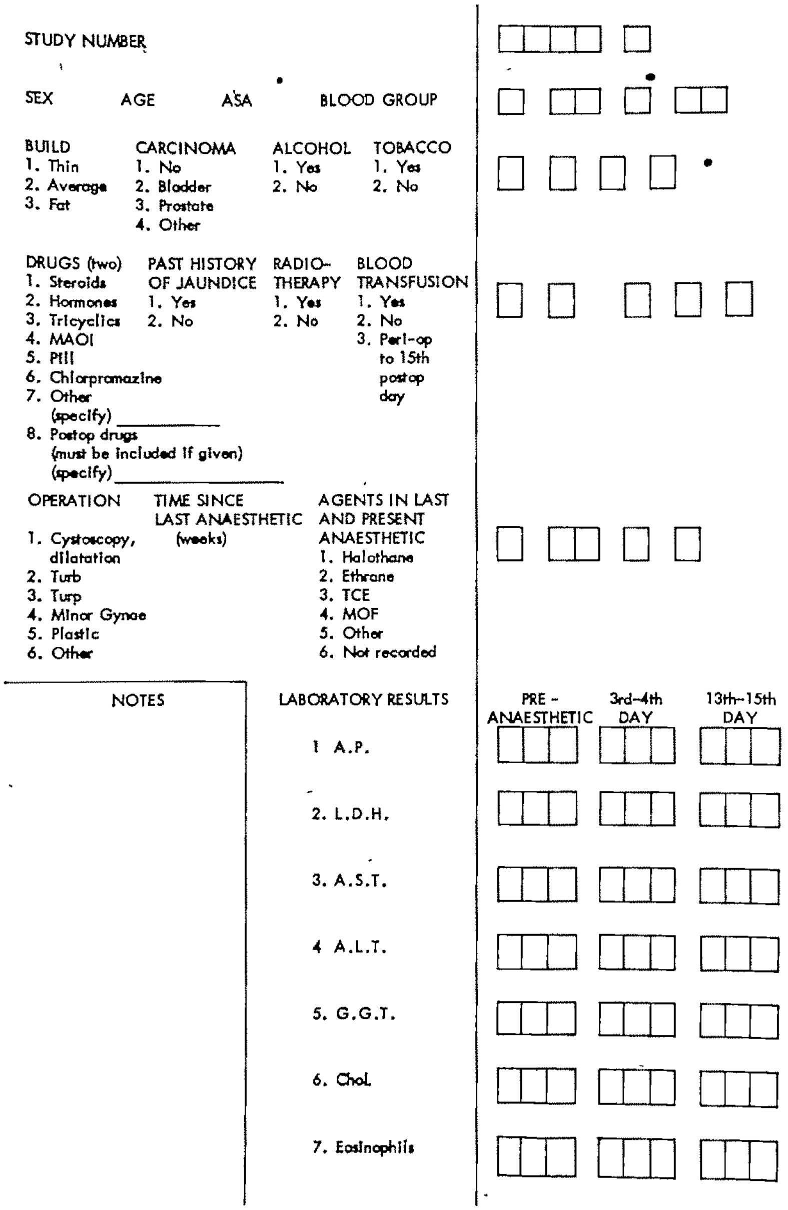


Study number ☐☐☐☐ ☐ Card 4

Postoperative complications: 1 Yes, 2 No, 9 Not Known

		4th day	15th day			4th day	15th day
1.	Usual sleep	☐	☐	18.	Pyrexia	☐	☐
2.	Usual appetite	☐	☐	19.	Jaundice	☐	☐
3.	Feel well	☐	☐	20.	Haemorrhage	☐	☐
4.	Feel awful	☐	☐	21.	Hypotension	☐	☐
5.	Nausea	☐	☐	22.	Breathlessness	☐	☐
6.	Vomiting	☐	☐	23.	PaO_2 <70	☐	☐
7.	Diarrhoea	☐	☐	24.	pH <7.35	☐	☐
8.	Constipation	☐	☐	25.	Thrombo-embolism	☐	☐
9.	Alert	☐	☐	26.	I.V. drip	☐	☐
10.	Confused/disorientated	☐	☐	27.	N.G. tube	☐	☐
11.	Unconscious	☐	☐	28.	ET tube	☐	☐
12.	Pain	☐	☐	29.	Myocardial infarction	☐	☐
13.	Anaemia	☐	☐	30.	Mechanical respiration	☐	☐
14.	Oliguria	☐	☐	31.	Cardiac arrest	☐	☐
15.	Infection	☐	☐	32.	Death	☐	☐
16.	Cough	☐	☐	33.	Ambulant	☐	☐
17.	Spit	☐	☐	34.	Other	☐	☐

FIG. 3. Chart for recording complications after operation.



STUDY NUMBER

SEX AGE ASA BLOOD GROUP

BUILD
1. Thin
2. Average
3. Fat

CARCINOMA
1. No
2. Bladder
3. Prostate
4. Other

ALCOHOL
1. Yes
2. No

TOBACCO
1. Yes
2. No

DRUGS (two)
1. Steroids
2. Hormones
3. Tricyclics
4. MAOI
5. Pill
6. Chlorpromazine
7. Other (specify) ____________
8. Postop drugs (must be included if given) (specify) ____________

PAST HISTORY OF JAUNDICE
1. Yes
2. No

RADIOTHERAPY
1. Yes
2. No

BLOOD TRANSFUSION
1. Yes
2. No
3. Peri-op to 15th postop day

OPERATION
1. Cystoscopy, dilatation
2. Turb
3. Turp
4. Minor Gynae
5. Plastic
6. Other

TIME SINCE LAST ANAESTHETIC (weeks)

AGENTS IN LAST AND PRESENT ANAESTHETIC
1. Halothane
2. Ethrane
3. TCE
4. MOF
5. Other
6. Not recorded

NOTES

LABORATORY RESULTS	PRE-ANAESTHETIC	3rd–4th DAY	13th–15th DAY
1 A.P.			
2. L.D.H.			
3. A.S.T.			
4 A.L.T.			
5. G.G.T.			
6. Chol.			
7. Eosinophils			

FIG. 4. Summary chart of biochemical and clinical data. A.P. = alkaline phosphatase; Chol. = serum cholinesterase.

using Technicon SMAC (Sequential Multiple Analyser with Computer). This gave readings for the concentrations of sodium, potassium, chloride, bicarbonate, urea, total protein, albumin, calcium, glucose, cholesterol, urate, creatinine, iron, triglycerides and total bilirubin. In addition, the serum concentrations of the following were available: alkaline phosphatase (ALP), lactate dehydrogenase (LDH), aspartate aminotransferase (AST or SGOT), alanine aminotransferase (ALT or SGPT) and creatine kinase (CPK). It was possible also to estimate serum cholinesterase (CHS) (Michel, 1949) and gamma glutamyl transferase (GGT) (Szasz, 1969). The Department of Haematology at the Royal Victoria Hospital provided a full haematological examination which included an eosinophil count.

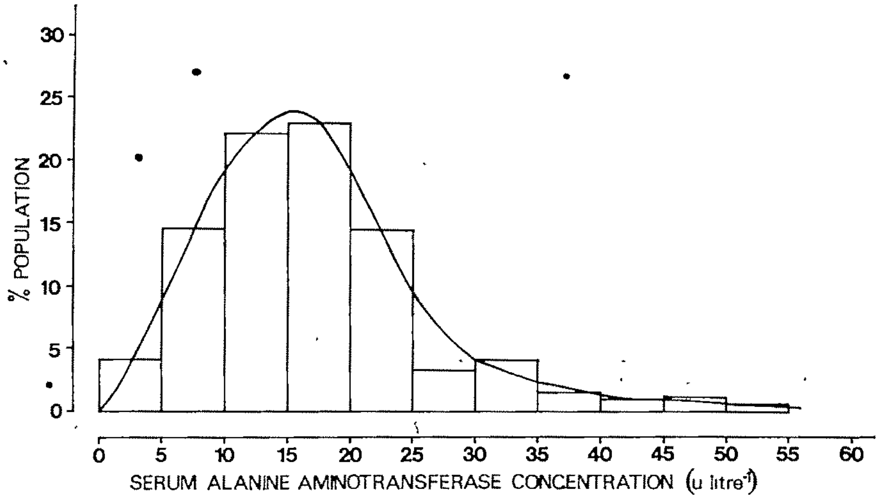


FIG. 5. Concentrations of alanine aminotransferase before operation.

Six enzymes were chosen specifically as indices of liver function. Serum alkaline phosphatase (ALP) reflects both damage to liver cells and biliary obstruction. Serum lactate dehydrogenase (LDH) is widely distributed throughout the body, with high concentrations in the heart, skeletal muscle, liver, kidney, brain and erythrocytes and consequently is increased in a wide variety of disease states. Serum aspartate aminotransferase (AST or SGOT) concentrations become increased in damage to the liver as well as skeletal and cardiac muscle. Serum alanine aminotransferase (ALT or SGPT) concentrations are more specifically related to liver cell damage than those of AST. Gamma glutamyl transferase (GGT) concentrations in serum originate primarily from the hepatobiliary system and are increased in all forms of liver damage. Serum cholinesterase (CHS) reflects liver cell dysfunction and is reduced in most forms of liver disease, especially those affecting protein synthesis. The eosinophil count was measured to reflect any hypersensitivity reaction.

Changes in the concentrations of the enzymes are known to be at a maximum within 3–4 days after any hepatic insult and should have decreased to their preoperative values within 2 weeks. Furthermore, as the clinical signs of "halothane hepatitis" are reported to be evident within 2 weeks after anaesthesia, it was decided that blood samples should be drawn before operation and on days 3–4 and 13–15 after operation. As far as possible these were taken at the same time each day, to eliminate changes which may have been attributable to diurnal variation. On each of the visits after operation a further clinical assessment of the patient's condition was made.

When the study had been in progress for about 1 year, the paucity of positive enzymatic evidence led us to doubt that the chosen enzyme tests were sufficiently sensitive to detect changes in liver function. However, concurrent studies in this department on the effect of ketamine infusions showed a sufficiently great frequency of changes in the enzyme concentrations (Dundee et al., 1980) to re-establish our confidence in the method.

IMMUNOLOGY

Walton and others (1976) have found a greater frequency of liver, kidney, microsomal and thyroid antibodies in association with unexplained hepatitis following halothane anaesthesia. As part of the study, a portion of each serum sample was stored at −20 °C, and detection and titration of auto-antibodies to smooth muscle, mitochondria, reticulum, gastric parietal cells, nuclei, thyroid colloid and thyroid microsomes were made using the indirect immunofluorescent technique. These were tested for in the three immunoglobulin classes IgG, IgA and IgM, at the Department of Immunology, Belfast City Hospital, and the results compared with base-line data from approximately 600 healthy persons of different ages and sexes.

ANALYSIS OF DATA

A summary chart of the biochemical and clinical data was prepared (fig. 4) and this formed the basis for the initial statistical analysis.

The distribution of enzyme concentrations in the overall population did not follow a Gaussian pattern, as is illustrated by the preoperative ALT values from the patients in the study (fig. 5). The statistical handling of the data was by two different approaches.

The first of these used a quantal method to measure the frequency of patients showing an "abnormal" increase in enzyme concentrations from the value before anaesthesia. The criterion for "abnormality" was that the value after anaesthesia would have changed by more than three standard deviations of the method of analysis from the value before anaesthesia. The standard deviation of the method of analysis was calculated from the coefficient of variation of several thousand repeat estimations on "control" sera over the period of the study and is expressed at the upper limit of the "normal" range. The "normal" enzyme ranges and corresponding standard deviations are as shown (table II). Chi-squared tests were carried out using this criterion.

TABLE II. *"Normal" enzyme concentration ranges and corresponding standard deviations of the method of estimation*

Liver function test	"Normal" range	SD
ALP	35–150 u. litre^{-1}	7 u. litre^{-1}
LDH	130–270 u. litre^{-1}	14 u. litre^{-1}
AST	10–40 u. litre^{-1}	7 u. litre^{-1}
ALT	10–45 u. litre^{-1}	7 u. litre^{-1}
GGT	5–34 u. litre^{-1}	4 u. litre^{-1}
CHS	50–110 Michel units	6 Michel units

The second method was an analysis of the enzyme concentrations before and after anaesthesia using appropriate parametric and non-parametric tests. Where applicable, the skew distribution of the enzyme concentrations was corrected by logarithmic transformation and analysis of variance and Student's paired *t* test used. Various non-parametric tests, including the Wilcoxon *T* test and the Mann-Whitney *U* test, were used on the non-transformed data.

Initially, the repeat halothane anaesthetics and the repeat enflurane anaesthetics were dealt with separately, and any statistically significant findings noted. The clinical sub-groups in each series were then analysed to see if there was any specific group of patients more prone to enzymatic changes than the overall study population. Those groups of patients having had a particular sequence of anaesthetics as outlined above were then considered. These were suitable for within-group analysis by the various statistical methods.

STAFF

This study required the continuous services of three full-time senior registrar anaesthetists and a biochemist as well as additional assistance from the staff of the University Department of Anaesthesia. This was in addition to laboratory, computer and secretarial personnel. It was under the supervision of two consultant anaesthetists, a consultant biochemist and a consultant immunologist.

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METHODOLOGIE D'UNE ETUDE SUR LES CHANGEMENTS SURVENANT DANS LES ENZYMES DU FOIE APRES L'ADMINISTRATION REPETEE D'AGENTS ANESTHESIANTS

RESUME

Cet article contient un rapport sur la méthodologie adoptée lors d'une importante étude sur l'influence de l'administration répétée d'agents anesthésiants sur la fonction hépatique, ainsi qu'une discussion sur les problèmes en cause. Les malades les plus appropriés sont ceux qui se présentent pour un examen endoscopique de la vessie et de l'urètre, pour une dilatation de l'urètre ou pour l'implantation cervicale de radium. On a pris des échantillons de sang immédiatement avant l'induction de l'anesthésie, les 3–4éme et 13–15ème jours après l'opération, moments où l'on a aussi procédé à une évaluation clinique du malade. On a choisi spécifiquement la mesure des concentrations de six enzymes pour servir d'indices de la fonction hépatique (lactate déshydrogénase, alcaline phosphatase, aspartate aminotransférase, alanine aminotransférase, cholinestérase du sérum et gamma glutamyl transférase). La numération des éosinophiles a été faite de manière à refléter toute réaction d'hypersensibilité. Leur répartition non conforme à la courbe de Gauss a nécessité l'usage de tests non paramétiques appropriés, et de tests paramétriques sur des données logarithmiques transformées. De plus on s'est servi d'une méthode de quantum pour mesurer la fréquence des malades accusant une augmentation "anormale" des concentrations d'enzymes.

METHODOLOGIE EINER PROSPEKTIVEN STUDIE VON LEBERENZYMVERÄNDERUNGEN AUF WIEDERHOLT VERABREICHTE NARKOSEMITTEL

ZUSAMMENFASSUNG

Ein Bericht uber diese Studie und die dabei auftretenden Probleme. Die geeignetsten Patienten waren die, bei denen es zu endoskopischen Untersuchungen von Blase und Harnleiter wegen Harnleiterdehnung und zervikaler Einpflanzung von Radium kam. Unmittelbar vor der Anästhesie wurden Blutproben abgenommen, und am 3.–4. und 13.–15. Tag nach der Operation, wenn auch eine klinische Beurteilung der Patienten vorgenommen wurde. Die Konzentrationen von sechs Enzymen (Laktatdehydrogenase, alkalische Phosphatase, Aspartataminotransferase, Alaninaminotransferase, Serumcholinesterase und Gammaglutamyltransferase) wurden speziell als Anzeiger der Leberfunktion ausgewählt. Ihre nichtgaussische Verteilung erforderte die Verwendung entsprechender nicht-parametrischer Tests zusammen mit parametrischen Tests von logarithmisch umgewandelten Daten. Zusätzlich wurde eine quantenmässige Methode benutzt, um die Häufigkeit zu messen, mit der es bei den Patienten zu einem "abnormen" Anstieg der Enzymkonzentrationen kam.

METODOLOGIA DE UN ESTUDIO EXPLORATORIO DE LAS ALTERACIONES DE LA ENZIMA HEPATICA A RAIZ DE ADMINISTRACIONES REPETIDAS DE ANESTETICOS

SUMARIO

Se da una reseña de la metodología usada en un amplio estudio exploratorio de la influencia de repetidas administraciones de anestéticos sobre la función hepática y se discuten los problemas que plantean. Los pacientes más adecuados eran los que se sometían a un examen endocoópico de la vejía y de la uretra, a una dilatación de la uretra y a una implantación cervical de radio. Se tomaron muestras de sangre justo antes de la inducción de la anestesia y en los días 3–4 y 13–15 después de la intervención, cuando se procedió también a una evaluación clínica del paciente. Las concentraciones de seis enzimas (dehidrogenasa de lactato, fosfatasa alcalina, aminotransferasa de aspartato, aminotransferasa de alanina, colinesterasa serosa y transferasa de glutamil gamma) fueron escogidas especialmente como índices de la funcíon hepática. Se midió la numeración eosinófila para reflejar cualquier reacción de hipersensibilidad. La distribución no-Gausiana de las mismas hizo necesario el uso de pruebas no-paramétricas apropiadas, junto con pruebas paramétricas en datos traspasados a logaritmos. Además, se usó un métado de tanteo para medir la frecuencia de un aumento "anormal" de las concentraciones enzimáticas en los pacientes.

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A PROSPECTIVE STUDY OF LIVER ENZYME AND OTHER CHANGES FOLLOWING REPEAT ADMINISTRATION OF HALOTHANE AND ENFLURANE

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SUMMARY

A prospective study of liver enzymes and other measurements following repeat administrations of halothane or enflurane was carried out in patients undergoing minor urological operations. The patient populations were similar with respect to frequency of factors which might influence liver function, social habits, drug therapy and time intervals between administrations. Sixty-three received two or more administrations of halothane and 66 received two or more administrations of enflurane, both drugs given with nitrous oxide in oxygen. There was a greater frequency of increased enzymatic activity following repeat administrations of halothane than following enflurane and the average alanine aminotransferase and gamma glutamyl transpeptidase concentrations were increased to a greater degree following halothane than enflurane. There was no change in the eosinophil count and no significant postoperative morbidity. Changes in alanine aminotransferase, lactate dehydrogenase and gamma glutamyl transpeptidase occurred more frequently in obese patients receiving halothane.

Disturbances of liver function are not uncommon in the period after operation and it is probable that surgery, coincidental viral hepatitis, changes in hepatic flow and concomitant drug therapy are usually more important causative factors than anaesthesia. However, on rare occasions a patient who is repeatedly exposed to halothane develops liver failure and jaundice for no apparent reason, the so-called "halothane hepatitis".

In 1974 the Medical Assessor to the Committee on Safety of Medicines sent a memorandum to anaesthetists in the United Kingdom stating that there was a greater risk of jaundice when halothane was given repeatedly within a period of a few weeks, than following a single exposure (Mansell Jones, 1974).

Inhalation anaesthetics are simple and safe to use, especially when the patient breathes spontaneously and they are often the agents of choice for minor procedures in outpatients for whom anaesthesia has frequently to be repeated. The medico-legal implications of the Assessor's edict placed the anaesthetist in a clinical dilemma, perhaps forcing him to use less suitable and less safe agents than halothane.

Enflurane was introduced to clinical practice some years ago and is now often used instead of halothane when repeated administrations are necessary. Although no instances of hepatitis have been reported in which enflurane could be solely incriminated, it will be remembered that a comparable situation existed in the past with regard to halothane. Because of these considerations, it was felt important to determine the extent of the relationship between repeated administration of halothane and enflurane, and the onset of hepatic dysfunction. A comprehensive prospective study appeared to provide the best means for obtaining this information.

We report the findings of a large prospective study of the effects of repeated administration of halothane or enflurane in a comparable patient population, during a 3-year period. Preliminary reports of this have been published by Dundee, Black and Neill (1979) and by Johnston and others (1979).

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METHODS

These have been described in detail by Fee and colleagues (1979) and McIlroy and colleagues (1979) and will only be summarized here. The subjects were mainly outpatients attending for minor urological operations and who had agreed to take part in the study. Detailed notes were made of the condition of the patient, using a computer-compatible form; included were previous anaesthetics, presence of idiosyncrasies, build, blood group, previous blood transfusions, alcohol and or tobacco intake and concurrent drug therapy. Anaesthesia was induced with thiopentone 4 mg kg^{-1} and continued with nitrous oxide in oxygen and either halothane or enflurane, with spontaneous ventilation from a semi-closed circuit. Random allocation was not possible because of the initial unavailability of enflurane. For this reason no statistical comparison between patients receiving halothane and enflurane was feasible.

Blood was sampled for biochemical analysis before induction of anaesthesia, and on days 3–5 (4) and 13–15 (14) after operation. The latter necessitated domiciliary visits when the general condition of the patient was noted on a specially prepared form. Blood was analysed with a Technicon SMAC (Sequential Multiple Analyser with Computer) which gave readings for electrolytes and several enzyme tests of liver function—serum alkaline phosphatase (ALP), lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT). In addition, serum cholinesterase (CHS) and gamma glutamyl transpeptidase (GGT) were estimated separately and a comprehensive haematological examination was obtained, including the eosinophil count. The range of normal values for the various tests is given in table V. An abnormal increase was taken as a value greater than mean + 3 SD of the method of estimation. For technical reasons, it was not always possible to perform all tests in each patient; the omissions are few, but they explain some discrepancy in numbers in tables XII and XIII.

Sera from four groups of patients with no evidence of malignant disease were tested for abnormal concentrations of autoantibodies. There were four patients in each group: group 1: no abnormal liver function tests; group 2: abnormal GGT; group 3: abnormal ALT; group 4: abnormal GGT and ALT. Base line data on the frequency and titres of these particular autoantibodies in approximately 600 healthy persons of different age and sex are available in the immunology laboratory.

The analysis of the data was based on the frequency of abnormal increases of the enzymes. Because of the skew nature of the distribution of enzymes, signifi-

TABLE I. *Physical characteristics of patients*

	Number of administrations							
	Halothane				Enflurane			
	2	3	4	5	2	3	4	5
No. of patients	63	22	10	4	66	26	10	4
Males	48	18	8	3	40	20	8	3
Age (yr)								
Mean ± SEM	61 ± 2	62 ± 3	59 ± 3	61 ± 5	63 ± 1	63 ± 2	59 ± 3	54 ± 6
60+	44	15	6	2	43	17	6	1
Build obese	15	6	3	2	16	4	1	0

TABLE II. *Factors which may influence liver function. Number of patients; % of group (table I) in brackets*

	Number of administrations							
	Halothane				Enflurane			
	2	3	4	5	2	3	4	5
History of jaundice	2 (3)	2 (9)	2 (20)	0	4 (6)	1 (4)	0	0
Carcinoma	41 (65)	15 (68)	8 (80)	3 (75)	50 (76)	18 (69)	7 (70)	2 (50)
Radiotherapy	14 (22)	5 (23)	3 (30)	1 (25)	19 (29)	5 (19)	1 (10)	1 (25)
Previous blood transfusion	14 (22)	8 (31)	5 (50)	0	16 (24)	5 (19)	1 (10)	0

cance of difference was calculated using the Wilcoxon matched-pairs signed ranks test and, after logarithmic transformation, the paired t test.

RESULTS

All the patients had a repeat administration of halothane or enflurane and were broadly comparable with respect to age, sex and build (table I), although it should be noted that 18 of the patients studied received both halothane and enflurane. The distribution of factors which may influence liver function is shown in table II, whilst social habits and drug therapy are indicated in table III. Table IV shows the time intervals between administrations.

The number of patients with liver function indices outside the accepted range of normal before the first anaesthetic is shown in table V.

TABLE III. *Social habits and concurrent drug therapy in the two groups of patients. Number of patients*

	Number of administrations					
	Halothane			Enflurane		
	2	3	4	2	3	4
Social habits						
Alcohol	37	14	6	30	14	4
Tobacco	33	12	4	32	14	5
Drug therapy						
Sedatives and analgesics	15	8	4	17	9	8
Cardiovascular	9	4	1	7	4	5
Antibiotics	3	4	0	3	0	0
Others	14	6	2	16	6	5

TABLE IV. *Time intervals between administrations. Number of patients*

	Number of administrations							
	Halothane				Enflurane			
	2	3	4	5	2	3	4	5
Time (weeks) from last anaesthetic								
1–2	10	0	2	1	13	3	0	0
3–4	4	0	0	1	3	0	0	0
5–10	14	3	3	1	7	2	2	0
11–30	35	19	5	1	43	21	8	4

TABLE V. *Percentage frequency of readings outside the accepted range of normal in the first blood sample before operation*

		Anaesthetic	
Test	Normal range	Halothane	Enflurane
ALP	35–105 u. litre^{-1}	6.8	4.5
LDH	130–270 u. litre^{-1}	10.3	12.1
AST	10–40 u. litre^{-1}	1.8	0
ALT	10–45 u. litre^{-1}	4.8	1.5
GGT	5–34 u. litre^{-1}	7.0	15.6
CHS	50–110 Michel Units	3.5	10.6
Eosinophils	0–400 μlitre^{-1}	5.9	5.3

TABLE VI. *Abnormal changes in enzymic activities and in eosinophil counts, 4 and 14 days after operation, following repeated administration of halothane. % of patients in each subgroup*

	Number of administrations									
	1		2		3		4		5	
	4	14	4	14	4	14	4	14	4	14
ALT	8	2	7	10	18	8	25	43	0	50
AST	4	2	4	4	7	0	0	0	0	0
GGT	0	2	20	28	28	21	33	28	50	67
ALP	0	2	0	6	6	0	10	0	25	33
LDH	6	4	16	12	22	7	38	29	25	0
CHS	4	2	17	14	44	29	33	0	75	100
Eosinophils	6	11	9	12	28	14	0	14	50	33

TABLE VII. *Abnormal changes in enzymic activities and in eosinophil counts, 4 and 14 days after operation, following repeated administrations of enflurane. % of patients in each subgroup*

	Number of administrations									
	1		2		3		4		5	
	4	14	4	14	4	14	4	14	4	14
ALT	2	4	9	4	0	0	0	0	0	0
AST	0	6	0	4	0	0	0	0	0	0
GGT	3	4	8	19	9	9	0	0	0	0
ALP	2	0	10	4	14	4	0	0	0	0
LDH	5	6	11	17	15	0	0	17	0	0
CHS	2	4	3	0	13	4	0	0	0	0
Eosinophils	13	13	17	18	13	27	0	0	0	0

It can be seen from tables VI and VII and figure 1 that disordered liver function tests were more frequent following repeated halothane anaesthesia than following enflurane, and this tendency was more pronounced as the number of administrations increased. The findings with ALT and GGT are further analysed in tables VIII–XI. Again, there is a greater frequency of significant changes with halothane than with enflurane. It is difficult to draw any firm conclusions from the eosinophil counts.

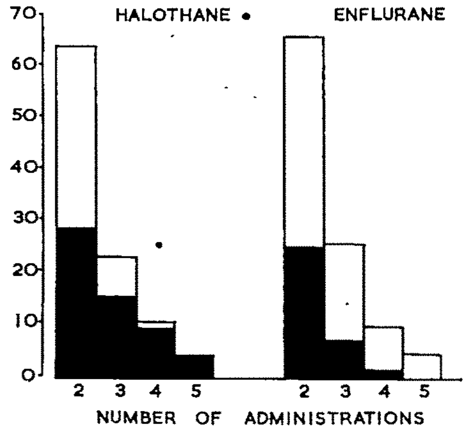

FIG. 1. Number of patients showing any abnormal liver function test (black) following repeat administration of halothane or enflurane. Column height indicates total number in each subgroup.

TABLE VIII. *Mean ALT and GGT values (after logarithmic transformation) of the samples obtained before the first operation (Pre-op.) and on days 3–5 (4) and 13–15 (14) following repeated administrations of halothane.* * $P < 0.05$ *as determined by paired t test*

No. of anaes-thetic	ALT			GGT		
	Pre-op.	Day 4	Day 14	Pre-op.	Day 4	Day 14
1	15.5	19.8*	17.9	10.4	11.1	11.2
2	15.7	18.8	20.9*	10.4	14.4*	17.2*
3	15.0	19.9	16.6	8.8	17.7*	15.7*
4	13.8	26.7	28.2*	8.8	18.6*	16.1*

TABLE IX. *Mean ALT and GGT values (after logarithmic transformation) of the samples obtained before the first operation (Pre-op.) and on days 3–5 (4) and 13–15 (14) following repeat administrations of enflurane*

No. of anaes-thetic	ALT			GGT		
	Pre-op.	Day 4	Day 14	Pre-op.	Day 4	Day 14
1	17.4	17.0	18.5	17.7	17.9	16.3
2	16.9	17.7	19.4	18.1	16.9	18.3
3	16.0	16.2	16.5	18.2	14.0	15.8
4	13.8	15.5	13.8	15.3	10.4	11.5

TABLE X. *Average ALT and GGT values in the sample obtained before the first operation (Pre-op.) and on days 3–5 (4) and 13–15 (14) following repeat administrations of halothane.* *$P < 0.05$ *as determined by the Wilcoxon matched-pairs signed-ranks test*

No. of anaes-thetic	ALT			GGT		
	Pre-op.	Day 4	Day 14	Pre-op.	Day 4	Day 14
1	18.8	28.3	23.1	12.3	13.3	13.2
2	18.9	27.3	28.3	12.4	17.9*	24.1*
3	16.1	59.9	18.4	9.7	26.6*	20.3*
4	15.2	59.0	29.1*	10.1	34.3*	20.1*

TABLE XI. *Average ALT and GGT values in the sample obtained before the first operation (Pre-op.) and on days 3–5 (4) and 13–15 (14) following repeat administrations of enflurane.* * $P < 0.05$ *as determined by the Wilcoxon matched-pairs signed-ranks test*

No. of anaes-thetic	ALT			GGT		
	Pre-op.	Day 4	Day 14	Pre-op.	Day 4	Day 14
1	19.1	19.4	23.1	22.0	22.1	22.0
2	18.8	21.2	22.3*	22.4	23.0	23.1
3	17.2	18.3	18.7	20.5	17.0	19.2
4	15.2	16.0	14.4	16.6	13.4	13.4

The influence of sex, obesity, alcohol and tobacco on the frequency of changes in four enzymes is shown in tables XII and XIII. There was a strikingly high frequency of abnormal liver function measurements in the obese patients who received halothane. This was not observed with enflurane. However, when the small number of obese women having either agent were considered there was a general tendency towards a greater frequency of enzymatic changes in this group compared with the population as a whole (table XIV). The only other statistically significant correlation was with smoking in the halothane series.

The immunological studies revealed no findings of any significance within any of the groups.

Postoperative morbidity

No patients became jaundiced following anaesthesia and there were no major increases in serum bilirubin concentration. Despite completion of a comprehensive questionnaire on the condition of the patient at each visit, the frequency of morbidity after anaesthesia was negligible and unrelated to the agent used. Two patients developed obvious episodes of bacteraemia, with rigors and sweating, and these were treated with antibiotics by the family doctors.

TABLE XII. *Number of patients with abnormal changes in enzymic activity on days 3–5 following administration of halothane, showing the influence of sex, obesity, alcohol and tobacco.* * *Statistically significant* ($P < 0.05$) *difference between two series*

	Number of administrations							
	AST		ALT		LDH		GGT	
	2	3	2	3	2	3	2	3
Males	1/41	1/13	2/40	2/13	5/42	3/14	6/40	4/14
Females	1/12	0/3	2/14	1/4	4/13	1/4	5/14	1/3
Non-obese	1/39	0/11	1/40	2/12	4/14	3/13	5/40	3/13
Obese	1/14	1/4	3/14*	1/5	5/14*	1/5	6/14*	2/5
Alcohol	2/32	0/9	3/32	2/11	5/33	2/11	6/32	5/11
Non-alcohol	0/21	1/6	1/22	1/6	4/22	2/7	5/22	0/7
					(Day 4) (Day 14)			
Tobacco	2/27	1/8	3/28	3/9	6/28 6/25*	3/9	5/26	2/9
Non-tobacco	0/26	0/7	1/26	0/8	3/27 0/26	1/9	6/28	3/9

TABLE XIII. *Number of patients with abnormal changes in enzymic activity on days 3–5 following administration of enflurane, showing the influence of sex, obesity, alcohol and tobacco*

	Number of administrations							
	AST		ALT		LDH		GGT	
	2	3	2	3	2	3	2	3
Males	0/37	0/17	2/36	0/16	3/32	2/14	2/38	1/17
Females	0/22	0/6	3/21	0/5	3/25	1/6	3/24	1/6
Non-obese	0/44	0/19	4/43	0/17	6/42	1/16	4/46	2/19
Obese	0/15	0/4	1/14	0/4	0/15	2/4	1/16	0/4
Alcohol	0/26	0/13	3/32	0/11	3/24	2/11	1/28	1/13
Non-alcohol	0/32	0/9	2/33	0/9	3/33	1/9	4/33	1/9
Tobacco	0/29	0/12	3/27	0/10	5/27	1/11	4/31	1/12
Non-tobacco	0/29	0/10	2/29	0/10	1/30	2/9	1/30	1/10

TABLE XIV. *Abnormal changes in enzymic activity (any test) or in eosinophil counts in obese, female patients*

	Number of administrations			
	Halothane		Enflurane	
	1	2	1	2
No. of patients	12	7	18	5
No. with increased activity	6	6	4	3

DISCUSSION

Assessing the likely development of clinical hepatitis by means of liver function tests may not be ideal, but it is the only practical method available. Liver biopsy may yield more positive information but for technical and ethical reasons it is not a feasible alternative. However, it seems reasonable to assume that the changes in serum enzyme concentrations which were found in the present study following repeated anaesthesia probably reflect some degree of hepatic injury, and it has been shown that such fluctuations may be associated with an increased risk of jaundice (Orlandi and Marubini, 1972).

As Zilva and Pannall (1975) have pointed out, two main pathological changes occur in most liver disorders: (a) liver-cell damage, with or without demonstrable liver dysfunction, and (b) cholestasis.

Either change or both may be present in a single disease. Liver-cell damage is detected by the measurement of the activities of plasma enzymes which have been released into the blood from the cells. Aspartate transaminase (AST) and alanine transaminase (ALT) are studied most commonly; activity of the latter is greater in cases of mild cellular damage. Cholestasis may be indicated by increased plasma activities of alkaline phosphatase, 5′-nucleotidase and gamma-glutamyltranspeptidase (GGT). The latter, however, is increased in about 90% of cases of all types of liver disorder (Rosalki, 1975) and the test is therefore useful in screening for liver disease. Our conclusions are based mainly on ALT and GGT results. True tests of liver function, that is its conjugating capacity (bromsulphthalein excretion) or its synthetic function (apart from measurement of cholinesterase activity), were not carried out because they are time-consuming and require a large volume of blood.

There have been several reported series of cases of jaundice associated with halothane (Inman and Mushin, 1974, 1978; Moult and Sherlock, 1975; Walton et al., 1976) but few prospective studies of the effects of repeated anaesthesia on hepatic function. These latter have given conflicting results. In two recent studies confined to women with carcinoma of the uterus requiring repeated anaesthesia for radium insertions, serum aspartate and alanine transaminase determinations were found to be increased in those patients receiving halothane but not in the non-halothane groups (Trowell, Peto and Crampton-Smith, 1975; Wright et al., 1975). Both suggest that women undergoing radiotherapy for carcinoma are especially prone to hepatic dysfunction after halothane anaesthesia and are a group in which repeated administrations of the agent should be avoided. Unfortunately, when these studies were performed, trichloroethylene and methoxyflurane were the only acceptable alternative inhalation agents and these are unpopular because of their clinical limitations. They did not appear to have a "homogeneous control" (non-halothane) series. The situation has changed with the recent introduction of enflurane, which has many of the advantageous features of halothane.

In a prospective study of hepatocellular function after repeated exposure to halothane or enflurane in 99 black women requiring radiation for cervical carcinoma, changes in serum transaminase concentrations were minimal and Allen and Downing (1977) concluded that, at least for this procedure, in their patient population, halothane and enflurane were equally safe. Likewise, McEwan (1976) did not find any significant changes with repeat administrations of halothane in male patients; in fact there were smaller disturbances of liver function after halothane than after the non-halothane anaesthesia.

The present investigation showed that a substantial number of patients undergoing urological surgery procedures who received halothane repeatedly within a short period of time developed abnormal liver function tests, and that this trend was more pronounced as the number of administrations increased. This did not occur to the same extent with enflurane. Halothane is metabolized in the liver by both oxidative (Van Dyke and Gandolfi, 1974) and reductive (Widger, Gandolfi and Van Dyke, 1976) pathways, the latter being more potentially hepatotoxic. Considerable increases in reductive metabolites have been demonstrated in both an animal model and clinical studies by Cousins and others (1976), in association with marked increases of ALT, and centralobular hepatic necrosis. Their work and that of Sharp, Trudell and Cohen (1979) provide strong evidence that halothane metabolism can cause direct cellular injury to the liver and could explain the increased enzyme concentrations observed in the present study.

It has been suggested that "halothane hepatitis" may be a manifestation of hypersensitivity to halothane or its metabolites because of suggestive clinical features and a high frequency of mitochondrial antibodies observed in some of the cases (Walton et al., 1976; Vergani et al., 1978). In spite of these reports, we found no evidence of a relationship between halothane, liver damage and immunological changes.

Abnormal liver function tests occur much more frequently than clinical hepatitis, and it is reasonable to suggest that these minor degrees of liver damage, caused by metabolism or immunological influences, form the basis for a development of "halothane hepatitis" in susceptible individuals.

In the current study a significantly greater frequency of disordered liver function occurred in obese subjects. It is of interest that clinical reports note a high frequency of jaundice in fat patients (Moult and Sherlock, 1975; Walton et al., 1976). Obesity may cause accumulation of halothane and its metabolites in the body. Slow release of the large amounts of halothane taken up by fat depots during anaesthesia may mean that there are excessive metabolic demands on the liver in the obese. Since the metabolism and excretion of halothane may be protracted, repeated administrations at short intervals could, in theory, lead to the production of greater amounts of intermediate metabolites than could be managed by the available liver microsomal enzyme systems (Carney and Van Dyke, 1972). One might postulate that these changes may be affected by tobacco smoking.

Extensive animal and clinical study has failed to detect any significant alteration in liver function following exposure to enflurane. In general, only minimal changes in serum transaminases, alkaline phosphatase and bilirubin were found (Lebowitz, Blitt and Dillon, 1970; Linde et al., 1970). In a recent study designed to determine comparative toxicities, suspensions of rat hepatocytes were incubated with varying concentrations of different halogenated anaesthetic agents (Stacey, Priestley and Hall, 1978). Toxicity, as determined by leakage of intracellular potassium and alanine aminotransferase, was most pronounced with chloroform and methoxyflurane, and significantly exceeded that of halothane after 20 min of incubation. Enflurane, however, did not affect potassium or alanine aminotransferase release, even after 60 min of incubation, at which time halothane toxicity was increased markedly. The toxic effects of halogenated inhalation anaesthetic agents, as measured in this *in vitro* preparation, appear to be of the same comparative order as their potential to cause clinical hepatotoxicity. Eger, Calverley and Smith (1976) found that prolonged periods of enflurane anaesthesia (9 MAC hours) in young fit volunteers caused only slight alterations in liver function tests.

A few clinical reports of impairment of liver function following enflurane anaesthesia have been published by Denlinger, Lecky and Nahrwold (1974) and by Sadove and Kim (1974), but in these it has not been possible to exclude the influences of factors such as virus hepatitis and blood tranfusion. In the present study deterioration of liver function following repeated enflurane anaesthesia did not occur more frequently in the obese than in the non-obese. This may be attributable to its lower fat solubility and less storage in the body.

The clinical implications of the biochemical changes observed in this study are difficult to assess. It must be assumed that halothane can cause disorders of liver function when given repeatedly within a short period of time, and there must be misgivings regarding its use in these circumstances particularly in obese patients. It is difficult to offer a satisfactory explanation for the conflict between the present findings and those of McEwan (1976) and Allen and Downing (1977), although different age, sex and race may be factors. However, it is an extremely useful and safe volatile anaesthetic and "halothane hepatitis" is very rare. Enflurane is a clinically acceptable alternative inhalation agent with which the likelihood of subclinical hepatic dysfunction occurring after repeated use is much less than with halothane.

Note added in proof. The discrepancy between numbers of patients having repeat anaesthetics in table I of the methodology paper (p. 1125) and in this paper results from the fact that the former paper included all patients, whether or not the adminstrations were within a period of 30 weeks.

In general, liver enzyme concentrations increased after anaesthesia had returned to within normal limits before subsequent administrations. However, they were more likely to be increased again in the same patients after the next anaesthetic.

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ETUDE DES CHANGEMENTS DANS LES ENZYMES DU FOIE ET DES AUTRES CHANGEMENTS QUI SURVIENNENT APRES L'ADMINISTRATION REPETEE D'HALOTHANE ET D'ENFLURANE

RESUME

On a procédé à une étude des enzymes du foie et pris diverses autres mesures après l'administration répétée d'halothane ou d'enflurane à des malades subissant des interventions urologiques mineures. Les populations de malades étaient similaires, en ce qui concerne la fréquence des facteurs susceptibles d'influencer la fonction hépatique, les habitudes sociales, le traitement par les médicaments et les intervalles de temps entre chaque administration. Soixante-trois personnes ont reçu au moins deux administrations d'halothane et 66 autres, au moins deux administrations d'enflurane, ces deux médicaments étant administrés en même temps que du protoxyde d'azote dans l'oxygène. On a constaté une plus grande fréquence d'activité enzymatique après l'administration répétée d'halothane qu'après l'administration d'enflurane; les concentrations moyennes de gamma glutamyl transpéptidase et d'alanine aminotransférase ont augmenté dans de plus fortes proportions après l'halothane qu'après l'enflurane. Il n'y a eu aucun changement dans la numération des éosinophiles et aucune morbidité postopératoire importante. Les changements dans l'alanine aminotransférase, la lactate déshydrogénase et la gamma glutamyl transpéptidase se sont produits plus fréquemment chez les patients obèses recevant de l'halothane.

EINE PROSPEKTIVE STUDIE VON LEBERENZYMEN UND ANDEREN VERÄNDERUNGEN NACH WIEDERHOLTEN VERABREICHUNGEN VON HALOTHAN UND ENFLURAN

ZUSAMMENFASSUNG

Diese Studien wurden an Patienten durchgefuhrt, die sich kleineren urologischen Operationen unterzogen. Die Patienten ähnelten einander bezüglich der Haufigkeit von die Leberfunktion beeinflussenden Faktoren wie Sozialgewohnheiten, Drogentherapie und Zeitintervalle zwischen Verabreichungen. 63 Patienten erhielten zwei oder mehr Dosen von Halothan, und 66 erhielten zwei oder mehr Dosen von Enfluran—beide Drogen zusammen mit Stickoxyd in Sauerstoff. Nach wiederholten Dosen von Halothan kam es zu häufigerem Auftreten verstärkter Enzymtatigkeit als auf Enfluran, und die Durchschnittskonzentrationen von Alaninaminotransferase und Gammaglutamyltranspeptidase wurden nach Halothan mehr erhoht als nach Enfluran. Es kam zu keiner Veranderung der Eosiniphilmenge und zu kainer wesentlichen postoperativen Morbiditat. Veränderungen von Alaninaminotransferase, Laktatdehydrogenase und Gammaglutamyltranspeptidase ergaben sich haufiger bei fettleibigen Patienten nach Halothan.

UN ESTUDIO EXPLORATORIO DE LA ENZIMA HEPATICA Y DEMAS ALTERACIONES CAUSADAS POR ADMINISTRACIONES REPETIDAS DE HALOTANO Y DE ENFLURANO

SUMARIO

Se llevó a cabo un estudio exploratorio de las enzimas hepáticas y otras mediciones a raíz de administraciones repetidas de halotano y de enflurano en pacientes sometidos a operaciones urológicas menores. Las poblaciones de pacientes eran similares con respecto a la frecuencia de los factores que pudiesen influenciar la función hepática, la costumbres sociales, la terapia con drogas e intervalos entre administraciones. Sesenta y tres pacientes recibieron dos o más administraciones de halotano y 66 dos o más administraciones de enflurano, ambas substancias administradas con óxido nitroso en oxígeno. A raíz de las administraciones repetidas de halotano, fue mayor la frecuencia de las actividades enzimáticas ampliadas que la de las actividades registradas con el enflurano, y después de la administración de halotano, las concentraciones medias de aminotransferasa de alanina y de transpeptidasa de glutamil gamma aumentaron en una proporción mayor que después de la administración de enflurano. No hubo ninguna alteración de la numeración eosinófila ni tampoco morbosidad postoperatoria significativa. Fueron más frecuentes las alteraciones de la aminotransferasa de alanina, de la dehidrogenasa de lactato y de la transpeptidasa de glutamil gamma en los pacientes obesos que recibían halotano.

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MORBIDITY AFTER DAY-CASE GYNAECOLOGICAL SURGERY

Comparison of enflurane with halothane

B. J. STANFORD, O. M. PLANTEVIN AND J. R. GILBERT

SUMMARY

In 105 patients undergoing day-case surgery recovery of consciousness was significantly faster after enflurane compared with halothane anaesthesia. There was no difference in postoperative morbidity between the two anaesthetic groups.

Enflurane has a significantly shorter recovery time than halothane (Govaerts and Sanders, 1975). We have compared enflurane with halothane as anaesthetic agents for outpatient surgery with reference to recovery time and postoperative morbidity in two groups. The frequency of minor complications during anaesthesia was noted also.

PATIENTS AND METHODS

One hundred and five consecutive patients (age range 21–59 yr, mean 39 yr) undergoing dilatation and curettage of the uterus as outpatients were studied. No premedication was given. Anaesthesia was induced with methohexitone in a dose sufficient to obtund the eyelash reflex, and maintained with 70% nitrous oxide in oxygen and either halothane or enflurane (allocated at random). The anaesthetics were given by the authors. A concentration of 2 MAC of the volatile agent was maintained until dilatation of the cervix was complete.

The duration of operation and the presence during anaesthesia of minor complications such as coughing, salivation, hiccup, laryngeal stridor and limb movement were noted.

Recovery of consciousness was assessed as the time at which the patient first opened her eyes in response to her name.

Before leaving hospital, each patient was asked to complete a questionnaire on the presence or absence of: headache, sore throat, nausea, vomiting, dizziness, drowsiness, muscle pain, backache and abdominal pain. A similar questionnaire was completed on the evening of the second day after operation, which sought the occurrence of the same symptoms on the evening of the day of operation and on the first and second days after operation. The patients were asked: "Could you perform normal duties on these two days? Would you have preferred to be an inpatient?" and whether they ate normal meals.

Student's *t* test was used to evaluate the significance of the difference in recovery times, and the Chi-square test was used to compare the minor complications noted during anaesthesia and the morbidity after operation.

RESULTS

The response rate was 98%. Two patients in the halothane group did not reply.

The groups were similar in respect of age, weight, dose of methohexitone, frequency of minor complications during anaesthesia (table I) and duration of operation (mean 7.4 min ± 1.9 SD for the enflurane group; 7.7 ± 1.8 SD min for the halothane group). However, those in the enflurane group recovered consciousness sooner after the end of the operation ($P < 0.01$). The mean interval between the end of surgery and the time of the patient's response to her name was 5.7 ± 2.8 SD min with enflurane and 7.6 ± 4.3 SD min with halothane.

TABLE I. *Minor complications during anaesthesia in two groups*

	Enflurane	Halothane
Number in group	53	52
Cough	15 (28%)	18 (35%)
Hiccup	22 (42%)	20 (38%)
Salivation	9 (17%)	14 (27%)
Laryngeal stridor	0 (0%)	4 (8%)
Limb movements	8 (15%)	9 (17%)

There were no significant differences in morbidity or life style after operation between the two groups

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TABLE II. *Morbidity after operation in two groups of patients. E = enflurane (53 patients); H = halothane (52 patients in hospital; 50 day 0, day 1 and day 2); day 0 = day of operation; day 1 = first day after operation; day 2 = second day after operation*

	In hospital		Day 0		Day 1		Day 2	
	E Total (%)	H Total (%)	E Total (%)	H Total (%)	E Total (%)	H Total (%)	E Total (%)	H Total (%)
Headache	16 (30)	23 (44)	24 (45)	24 (48)	17 (32)	18 (36)	6 (11)	13 (26)
Sore throat	1 (2)	2 (4)	1 (2)	6 (12)	1 (2)	5 (10)	3 (6)	5 (10)
Vomiting	0 (0)	5 (10)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)
Nausea	6 (11)	11 (21)	16 (30)	12 (24)	3 (6)	6 (12)	2 (4)	2 (4)
Dizziness	13 (25)	17 (33)	11 (21)	12 (24)	8 (15)	6 (12)	8 (15)	6 (12)
Drowsiness	23 (43)	20 (38)	37 (70)	27 (54)	15 (28)	14 (28)	4 (8)	6 (12)
Muscle aches	10 (19)	5 (10)	8 (15)	7 (14)	7 (13)	12 (24)	2 (4)	7 (14)
Backache	20 (38)	20 (38)	23 (44)	20 (40)	23 (44)	21 (42)	19 (36)	16 (32)
Slight abdominal pain	35 (66)	28 (54)	34 (64)	27 (54)	26 (49)	31 (62)	16 (30)	23 (46)
Severe abdominal pain	1 (2)	2 (3)	2 (4)	4 (8)	3 (6)	2 (4)	4 (8)	0 (0)
Able to eat normal meals			45 (85)	39 (78)	51 (96)	48 (96)	49 (92)	49 (98)
Unable to perform normal duties					21 (42)	21 (44)	14 (26)	9 (20)
Normal duties not stated					3	2	4	4

at any time (table II). The most frequent symptoms were abdominal pain, backache, drowsiness and headache. Fifteen per cent of each group would have preferred to have been treated as inpatients.

DISCUSSION

We found that the time of recovery from anaesthesia was significantly shorter after enflurane than after halothane, thus confirming the work of Govaerts and Sanders (1975). Korttila and colleagues (1977) found that recovery of driving skills was faster after enflurane compared with halothane. This faster recovery may be an advantage in a busy unit with a limited number of recovery nurses.

Towey and co-workers (1979) showed that induction of anaesthesia with Althesin for day-case surgery led to a faster recovery than did induction with thiopentone, but the problem of possible hypersensitivity to Althesin has to be weighed against the advantage of rapid recovery. In the present study methohexitone was the induction agent as this has also been found to produce faster initial recovery from anaesthesia than thiopentone (Korttila et al., 1975).

Dobkin and colleagues (1969) commented on the absence of breath-holding, salivation, laryngospasm and coughing with enflurane, but in the present study no significant difference from halothane was found, although it was our clinical impression that enflurane was easier to administer than halothane. Spontaneous limb movements, sometimes associated with enflurane, were not seen in this study, presumably because the depth of anaesthesia associated with such an effect was not reached.

Fahy and Marshall (1969) and Towey and others (1979) demonstrated a high frequency of postoperative symptoms after day-case surgery, some of which persist into the second day after operation. Hunt, Plantevin and Gilbert (1979) showed that a technique of anaesthesia using methohexitone and fentanyl reduced significantly the frequency of backache in the first few hours after operation, and of abdominal pain later on the day of operation, but had no effect on morbidity on the first and second days after operation, when compared with halothane. The present study confirmed a high morbidity rate after outpatient gynaecological surgery and showed that this was not influenced by the use of enflurane as opposed to halothane anaesthesia.

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MORBIDITE APRES CHIRURGIE GYNECOLOGIQUE EFFECTUEE SANS SEJOUR A L'HOPITAL

Comparaison de l'enflurane et de l'halothane

RESUME

Sur 105 malades subissant une intervention chirurgicale sans séjour hospitalier, la reprise de conscience a été nettement plus rapide après une anesthésie à l'enflurane qu'après une anesthésie à l'halothane. Il n'y a eu aucune différence dans la morbidité post-opératoire entre les deux groupes de personnes anesthésiées.

MORBIDITÄT NACH AMBULANTEN GYNÄKOLOGISCHEN EINGRIFFEN

ZUSAMMENFASSUNG

Bei 105 Patientinnen mit ambulant vorgenommenen Eingriffen wurde das Bewusstsein wesentlich rascher nach Enfluran- als nach Halothannarkose wiedererlangt. In der postoperativen Morbidität gab es zwischen diesen beiden Narkosegruppen keine Unterschiede.

MORBOSIDAD DESPUES DE CIRUJIA GINECOLOGICA AMBULATORIA

Comparacian del enflurano con el halotano

SUMARIO

En 105 pacientes sometidos a cirujía ambulatoria, la recuperación del conocimiento fue significativamente mucho más rápida con la anestesia por enfluorano que con la por halotano. No hubo ninguna diferencia en la morbosidad postoperatoria entre los dos grupos de anestéticos.

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LOCAL COMPLICATIONS OF THIOPENTONE INJECTION

A further report

D. DENISON DAVIES

SUMMARY

Cases of local complications following the injection of thiopentone and reported to the Medical Defence Union and to the Medical Protection Society in the period 1970–77 were analysed. There was no case of gangrene distal to the site of injection, but two cases of isolated damage to nerves, muscles and tendons and two cases of local tissue necrosis at the site of injection. A comparison of the results of the present investigation with those of two previous investigations indicates that the frequency of such complications has diminished over the period 1957–77.

Two previous studies of local complications of thiopentone injections (Davies, 1966, 1971) were confined to cases of local tissue necrosis, damage to nerves, muscles and tendons, and of gangrene. In the first report the cases were those that had been reported to the Medical Defence Union during the period 1957–63 (inclusive); in the second the cases were those reported to the Medical Defence Union or to the Medical Protection Society during 1964–69 (inclusive).

A third investigation of such local complications reported to the Medical Defence Union or to the Medical Protection Society during the period 1970–77 (inclusive) has been undertaken. Brief records of the cases are presented.

The investigation has not been concerned with the complication of venous thrombosis following injection.

CASE REPORTS

Gangrene distal to the site of injection

No such cases were reported.

Two cases of isolated damage to nerves, muscles and tendons

Case 1. Thiopentone (5% solution) was injected by a student (under the supervision of a Consultant Anaesthetist) into the antecubital fossa of a woman aged 30 yr who was to undergo a minor gynaecological procedure. Towards the end of the injection the patient flexed her arm so the needle was immediately withdrawn. Three hours after operation the patient complained of pain in the arm. The following day she was seen by a vascular surgeon who found the ulnar pulse to be absent. A fasciotomy of the sublimis muscle was performed and the muscle was found to be ischaemic. Three months later recovery of the arm was considered to be complete.

Case 2. Thiopentone (2.5% solution) was injected via an indwelling needle into a vein on the back of the hand. A few millilitre of solution were injected outside the vein and a swelling was noticed. The indwelling needle was withdrawn. It was suspected that the extensor tendons on the dorsum of the hand had been damaged. An exploratory operation was carried out and it was found that there was much scarring around the tendons. The patient was left with restricted flexion of all four fingers.

Two cases of tissue necrosis at the site of injection

Case 3. Thiopentone (5% solution) was injected into the forearm. A quantity of solution was administered extravenously. Some soft tissue damage at the site of the injection was produced. There developed an ulcerated area; a small skin graft had to be applied to this.

Case 4. Thiopentone (2.5% solution) was injected extravenously into the tissues on the back of the hand. Approximately 4 ml of solution were given. Subsequently a small area of skin sloughed; this required a skin graft.

COMPARISON WITH PREVIOUS INVESTIGATIONS

A summary of the results of the present investigation and of the two previous investigations is given in table I. The first investigation was concerned with

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TABLE I. *Summary of the results of three investigations into local complications of thiopentone injection (numbers of cases)*

	First investigation (Davies, 1966)	Second investigation (Davies, 1971)	Third (present) investigation
	Medical Defence Union only 1957–63 (7 years)	Medical Defence Union and Medical Protection Society 1964–69 (6 years)	Medical Defence Union and Medical Protection Society 1970–77 (8 years)
Gangrene	3	none	none
Damages to nerves, muscles and tendons	5	3	2
Local tissue necrosis	10	4	2

cases reported to only one of the medical defence organizations (Medical Defence Union). The second investigation was concerned with cases reported to two organizations (Medical Defence Union and Medical Protection Society). The present investigation also was concerned with cases reported to the two organizations.

DISCUSSION

There was a reduction in the number of complications reported when compared with the second investigation (Davies, 1971) which, in turn, showed a marked reduction in the number reported when compared with the first investigation (Davies, 1966). Figures given in each of the investigations cannot, however, be used to evaluate the total frequency throughout the country of a particular complication, as only the more serious cases would have been reported to the defence organizations; nevertheless, the three investigations should be roughly comparable and the progressive diminution in the number of cases reported in each category of complication probably does reflect a real diminution in frequency of the complications throughout the country.

It is noteworthy, once again, that in the present investigation (as in the second investigation) there were no reports of gangrene developing distal to the site of injection. This is confirmation that such complication is now rare.

The diminishing frequency of local complications is probably attributable to several factors. An increasing awareness by anaesthetists of the possibilities of such complications has led, no doubt, to increasing care being exercised during injection. Also of importance is the fact that the 5% solution of thiopentone is being increasingly replaced by the 2.5% solution (table II). The 2.5% solution clearly cannot be regarded as completely innocuous; however, animal studies have shown that, so far as the production of gangrene as a result of intra-arterial injection is concerned, the 2.5% solution is very much less damaging than the 5% solution (Kinmonth and Shepherd, 1959).

TABLE II. *Percentages of thiopentone, supplied to the home market by May & Baker Ltd, specifically for constitution into 5% solution and into 2.5% solution respectively (K. M. Youings, personal communication)*

Period	For 2.5% solution (percentage)	For 5% solution (percentage)
1962–63	35	65
1968–69	72	28
1979 (estimate)	94	6

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COMPLICATIONS LOCALES APRES UNE INJECTION DE THIOPENTONE

Rapport supplémentaire

RESUME

Nous avons analysé certains cas, où des complications locales ayant suivi une injection de thiopentone ont été signalées au Medical Defence Union et à la Medical Protection Society au cours de la période comprise entre 1970–77. Il n'y a eu aucun cas de gangrène éloigné du point d'injection; mais on a enregistré deux cas de dommages isolés aux nerfs, muscles et tendons et deux cas de nécrose

des tissus locaux au point d'injection. La comparaison des résultats découlant de ces recherches et de ceux de deux études précédentes indique que la fréquence des complications de ce genre a cependant diminué au cours de la période 1957–77.

LOKALE KOMPLICATIONEN NACH THIOPENTON-INJEKTIONEN

Ein weiterer Bericht

ZUSAMMENFASSUNG

Analysiert wurden Falle lokaler Komplikationen nach Thiopenton-Injektionen, die der Medical Defence Union und der Medical Protection Society von 1970 bis 1977 gemeldet wurden. Es gab keinen Fall von Nekrose distal von der Injektionsstelle, aber zwei Fälle von isolierter Nerven-, Muskell-, und Sehnenschädigung, sowie Fälle von lokaler Gewebenekrose an der Injektionsstelle. Ein Vergleich der gegenwärtigen Untersuchungsresultate mit denen zweier voriger Untersuchungen zeigt, dass die Häufigkeit solcher Komplikationen in der Periode zwischen 1957–77 gesunken ist.

COMPLICACIONES LOCALES DEBIDAS A INYECCIONES DE TIOPENTONA

Un estudio adicional

SUMARIO

Se procedió a un análisis de casos de complicaciones locales a raíz de la inyección de tiopentona, los que fueron referidos a la Unión de Defensa Médica y a la Asociación para la Protección Médica durante el periodo 1970–77. No hubo caso de gangreno distal al lugar de inyección, pero sí dos casos de lesión aislada a los nervios, músculos y tendones y dos casos de necrosis del tejido en el punto de inyección. Una comparación de los resultados de la investigación actual con los de las investigaciones anteriores demuestra que la frecuencia de tales complicaciones disminuyó durante el periodo 1957–77.

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COMPARISON OF ETOMIDATE IN COMBINATION WITH FENTANYL OR DIAZEPAM, WITH THIOPENTONE AS AN INDUCTION AGENT FOR GENERAL ANAESTHESIA

K. KORTTILA, T. TAMMISTO AND U. AROMAA

SUMMARY

In 104 premedicated patients undergoing general surgery, anaesthesia was induced either with etomidate 0.3 mg kg^{-1} preceded by fentanyl 1.25 or 2.5 $\mu g\ kg^{-1}$ i.v. or diazepam 0.0625 or 0.125 mg kg^{-1} i.v., or with thiopentone preceded by fentanyl 1.25 $\mu g\ kg^{-1}$ i.v. Despite the use of fentanyl or diazepam, the frequency of pain on injection in patients receiving etomidate was between 32% and 53%, being rated as severe in 5–20% of patients. No pain was experienced by patients receiving thiopentone. The frequency of involuntary movement was 15–35% with etomidate and 15% with thiopentone. The frequency of both pain and involuntary muscle movements was least when fentanyl 2.5 $\mu g\ kg^{-1}$ preceded the administration of etomidate. There was no significant relationship between the pain and muscle movement; three of 10 patients given etomidate into a central vein had such movements.

Pain during injection and involuntary muscle movement (Morgan, Lumley and Whitwam, 1975; Ghoneim and Yamada, 1977; Lees and Hendry, 1977; Schuermans et al., 1978) have restricted the popularity of etomidate as an i.v. anaesthetic agent. Fentanyl i.v. has been reported to alleviate the pain (Schuermans et al., 1978), and oral diazepam to decrease the frequency of involuntary muscle movement (Holdcroft et al., 1976). The use of polyethylene glycol or propylene glycol as a vehicle for etomidate has been reported also to produce less pain on injection than etomidate in an aqueous form (Van Dijk, 1978; Zacharias et al., 1978).

We have compared etomidate dissolved in propylene glycol, preceded by fentanyl or diazepam administered i.v., with thiopentone as an induction agent for balanced general anaesthesia. Pain and involuntary muscle movements and changes in arterial pressure and heart rate during the induction period were recorded.

PATIENTS AND METHODS

Patients and anaesthesia

Eighty-four patients undergoing abdominal, urological or varicose vein surgery were studied. All were in good general health. According to the rating of Dundee, Moore and Nicholl (1962), slight to moderate drowsiness was noted after premedication, which consisted of atropine 0.01 mg kg^{-1} plus oxycodone chloride (Oxanest, Leiras, Turku) 0.13 mg kg^{-1}, with promethazine chloride (Lergigan, Neofarma, Kuopio) 12.5–50 mg given i.m. 20 and 40–60 min before the induction of anaesthesia, respectively.

An i.v. cannula (Vygon, Paris, diameter 1.6 mm) was inserted into the largest forearm vein of all but two or three patients, in whom a vein in the dorsum of the hand was used. The injections of tubocurarine 3–5 mg (Tubocurarin, Orion, Helsinki) and fentanyl (Fentanyl, Orion, Helsinki) 1.25 or 2.5 $\mu g\ kg^{-1}$ or diazepam (Diapam, Orion, Helsinki) 0.0625 or 0.125 mg kg^{-1} were given i.v. over 30 s in a double-blind, randomized fashion (table I). Two minutes later, anaesthesia was induced with etomidate dissolved in 35% propylene glycol (Etomidate 2 mg ml^{-1}, Janssen, Beerse), 0.3 mg kg^{-1} being injected in 30 s; tracheal intubation was facilitated with suxamethonium 1.5 mg kg^{-1} (Sukolin, Orion, Helsinki); and anaesthesia was maintained with 66% nitrous oxide in oxygen given in a semi-open system with controlled ventilation. Minute volume was adjusted with the aid of an end-tidal carbon dioxide analyser to keep Pa_{CO_2} in the normal range. Tubocurarine was given to maintain neuromuscular blockade; 20–25% of the patient's muscle power was maintained as assessed with a neurostimulator (Ali and Savarese, 1976). Fentanyl was given to provide adequate analgesia. At the end of anaesthesia, atropine 1 mg and neostigmine 2 mg (Metastigmin, Star, Tampere) were given i.v. and the administration of nitrous oxide was

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TABLE I. *Characteristics of the groups, drug doses and duration of anaesthesia (means ± SD)*

Induction	No. of patients (F/M)	Age (yr)	Weight (kg)	Height (cm)	Duration of anaesthesia (min)
Fentanyl 1.25 μg kg^{-1} + etomidate 0.3 mg kg^{-1}	21 (15/6)	49 ± 12	66 ± 11	167 ± 9	100 ± 62
Fentanyl 2.5 μg kg^{-1} + etomidate 0.3 mg kg^{-1}	22 (10/12)	43 ± 17	69 ± 14	168 ± 13	85 ± 41
Diazepam 0.0625 mg kg^{-1} + etomidate 0.3 mg kg^{-1}	20 (10/10)	38 ± 15	70 ± 13	172 ± 9	91 ± 42
Diazepam 0.125 mg kg^{-1} + etomidate 0.3 mg kg^{-1}	21 (12/9)	42 ± 16	66 ± 15	168 ± 10	96 ± 57
Fentanyl 1.25 μg kg^{-1} + thiopentone 3 mg kg^{-1}	20 (9/11)	41 ± 13	68 ± 12	170 ± 9	108 ± 67

stopped as soon as the patient recovered muscle power to the extent that train-of-four stimulae indicated no decrease in response (Ali and Savarese, 1976). After wakening, the patients were transferred to the recovery room.

Twenty patients with characteristics similar to those described above were premedicated and anaesthetized in the same manner, but fentanyl 1.25 μg kg^{-1} followed by thiopentone 3 mg kg^{-1} was given for induction. All the i.v. injections were made into a rapidly running Ringer's lactate infusion solution (Fysiosol, Leiras, Turku). Informed consent was obtained from each patient for the procedure.

General assessment

Drowsiness was assessed 2 min after the injection of fentanyl or diazepam as follows: none = awake; slight = asleep, communicates easily; moderate = asleep, tries to communicate; severe = asleep, does not try to communicate.

Two minutes after the injection of etomidate or thiopentone, the eyelash reflex and reactions to surface pain (response to pinching lower abdomen with forceps) were tested. If the eyelash reflex was present and the anaesthetist considered the patient to be inadequately anaesthetized, etomidate 5 mg or thiopentone 50 mg was given before intubation.

Assessment of pain during injection and of involuntary muscle movements

The patients were asked during the injection of etomidate or thiopentone: "Do you feel something unusual in your arm?" A burning sensation or pain was considered as slight pain. Grimacing or vocalization was rated as severe pain. Involuntary muscle movements during induction were rated none, slight, moderate (similar to suxamethonium-induced fasciculations), marked (need for restraint), severe (tonic or clonic convulsions).

The relationships between the degree of drowsiness, age and pain during injection and the frequency of involuntary movements were determined.

So that the frequency of muscle movements could be evaluated more accurately in patients not experiencing pain during the injection, another 10 patients with characteristics similar to the others were given etomidate 0.3 mg kg^{-1} into a central venous cannula without prior administration of fentanyl or diazepam.

Arterial pressure and heart rate

Systolic and diastolic arterial pressures were measured by auscultation (Chamberlain and Ogilvie, 1967), and heart rate was recorded from an electrocardiographic monitor. Measurements were taken before the initial dose of tubocurarine, 2 min after the administration of fentanyl or diazepam (before the induction agent), 2 min after the injection of the etomidate or thiopentone, immediately after tracheal intubation, and before the incision.

General rating of anaesthesia

The quality of the anaesthesia was rated as poor, fair or good; the last rating represented smooth maintenance and rapid awakening.

Statistical analysis

Analysis of variance was used to compare arterial pressure and heart rate changes. Other assessments were compared with the Chi-square test because of the non-parametric nature of the data.

RESULTS

General assessment

Patients given diazepam were moderately to severely drowsy, whereas those receiving fentanyl were only slightly drowsy ($P < 0.001$; table II).

Assessments during the induction of anaesthesia and the frequency of additional doses of etomidate or thiopentone are shown in table III. The eyelash reflex was present more often ($P < 0.01$) after the smaller dose of fentanyl than after diazepam. Reactions to abdominal pinching were most frequent after thiopentone. Patients tolerated the presence of the endotracheal tube best (77%) when fentanyl 2.5 $\mu g\ kg^{-1}$ was given before the etomidate and worst (15%) when diazepam 0.0625 $mg\ kg^{-1}$ was given before etomidate. None of the patients given the larger doses of fentanyl or diazepam needed more than the initial 0.3 $mg\ kg^{-1}$ of etomidate before intubation, while three patients who were given the smaller dose of fentanyl and one patient who was given the smaller dose of diazepam needed more. However, eight patients (40%) who were given the 3-$mg\ kg^{-1}$ dose of thiopentone after fentanyl 1.25 $\mu g\ kg^{-1}$ needed more thiopentone to induce sleep.

Pain and involuntary muscle movements

None of the patients receiving thiopentone reported pain during its injection, while 32–53% of the patients given etomidate did so ($P < 0.01$). The nature of pain was generally slight, but depending on the preceding adjuvant, it was rated as severe by 5–20% of the patients (table IV).

Involuntary muscle movements were commonest in patients who received diazepam before etomidate (29–35%), and in 5% of all the patients given etomidate, the movements were severe and required restraint.

No significant relationships were noticed between the patient's degree of drowsiness, age, or the frequency of pain during the injection and the frequency of involuntary muscle movements (table V). However, such movements were twice as common in patients slightly or moderately drowsy, in those patients under the age of 60 yr or in patients who reported pain during the injection, compared with

TABLE II. *Drowsiness after the injection of diazepam or fentanyl before induction (% of total)*
*χ^2-test between groups: *$P < 0.001$; †preceding etomidate; ‡preceding thiopentone*

Adjuvant	No. of patients	Drowsy (% of patients)			
		None*	Slight	Moderate	Severe
Fentanyl 1.25 $\mu g\ kg^{-1}$†	21	29	57	14	0
Fentanyl 2.5 $\mu g\ kg^{-1}$	22	9	77	9	5
Diazepam 0.0625 $mg\ kg^{-1}$	20	5	25	70	0
Diazepam 0.125 $mg\ kg^{-1}$	21	0	24	48	28
Fentanyl 1.25 $\mu g\ kg^{-1}$‡	20	35	65	0	0

TABLE III. *Eyelash reflex, reaction to abdominal pinching, and toleration of tracheal tube (% of total)*
*χ^2-test between groups: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$*

Induction	Positive eyelash reflex	Reaction to pinching				Tube not tolerated**	Patients given more induction agent***
		None*	Slight	Moderate	Severe		
Fentanyl 1.25 $\mu g\ kg^{-1}$ + etomidate 0.3 $mg\ kg^{-1}$	43	19	14	0	5	52	14
Fentanyl 2.5 $\mu g\ kg^{-1}$ + etomidate 0.3 $mg\ kg^{-1}$	18	23	14	5	5	23	0
Diazepam 0.0625 $mg\ kg^{-1}$ + etomidate 0.3 $mg\ kg^{-1}$	5	35	10	20	5	85	5
Diazepam 0.125 $mg\ kg^{-1}$ + etomidate 0.3 $mg\ kg^{-1}$	0	33	19	5	9	62	0
Fentanyl 1.25 $\mu g\ kg^{-1}$ + thiopentone 3 $mg\ kg^{-1}$	40	65	10	35	20	65	40

TABLE IV. *Frequency of pain during the injection and involuntary muscle movements during induction (% of total).* χ^2*-test between groups;* **P* < 0.001; †χ^2*-test between groups, not significant*

Induction	Pain			Involuntary muscle movements			
	Total*	Slight	Severe	Total†	Slight	Moderate	Severe
Fentanyl 1.25 μg kg^{-1} + etomidate 0.3 mg kg^{-1}	53	43	10	19	0	14	5
Fentanyl 2.5 μg kg^{-1} + etomidate 0.3 mg kg^{-1}	32	27	5	15	5	5	5
Diazepam 0.0625 mg kg^{-1} + etomidate 0.3 mg kg^{-1}	45	25	20	35	15	15	5
Diazepam 0.125 mg kg^{-1} + etomidate 0.3 mg kg^{-1}	53	48	5	29	14	10	5
Fentanyl 1.25 μg kg^{-1} + thiopentone 3 mg kg^{-1}	0	0	0	15	10	5	0

those patients who were more drowsy, who were older or who did not feel pain during the injection.

Three out of the 10 patients who were given etomidate 0.3 mg kg^{-1} into a central vein had involuntary muscle movements without any feelings of pain during injection. In one of the patients, the movements were rated as severe.

TABLE V. *Relationship of drowsiness, age and pain during the injection to the frequency of involuntary muscle movements in patients injected with etomidate* (n = 84)

Variable	No. of patients	Movements (%)
Fatigue induced by premedication and the adjuvant drug preceding etomidate:		
None or slight	56	30
Moderate or severe	28	14
Age of patient:		
Less than 60 yr	66	29
60 yr or more	18	11
Existence of pain during the injection:		
No	46	17
Yes	38	34

Arterial pressure and heart rate

There were no significant differences between the groups in systolic arterial pressure when measured after the injection of diazepam or fentanyl, after the induction agent, or before the incision (fig. 1). The increase in systolic arterial pressure following intubation differed significantly ($P < 0.01$) between the groups. The increase averaged 25 mm Hg in patients given the smaller dose of fentanyl before etomidate or thiopentone; it averaged less than half that in those patients given the larger dose of diazepam before etomidate. The changes in heart rate and diastolic arterial pressure resembled the changes in systolic arterial pressure (fig. 1).

General acceptability of anaesthesia

On the anaesthetist's rating of the quality of anaesthesia (table VI), there were no differences for these variables between groups.

The commonest reasons for not rating these variables as good were: (1) induction: pain or involuntary movements with etomidate; need to give more induction agent with thiopentone; (2) maintenance: greater than usual need to supplement nitrous oxide with either etomidate or thiopentone;

TABLE VI. *Anaesthetist's rating of the quality of anaesthesia, maintenance and awakening (% of total). P = poor; F = fair; G = good (for explanation, see text).* *χ^2*-test between groups, not significant*

Induction	Induction*			Maintenance*			Awakening*		
	P	F	G	P	F	G	P	F	G
Fentanyl 1.25 μg kg^{-1} + etomidate 0.3 mg kg^{-1}	9	29	62	0	24	76	0	14	86
Fentanyl 2.5 μg kg^{-1} + etomidate 0.3 mg kg^{-1}	0	9	91	0	5	95	5	27	68
Diazepam 0.0625 mg kg^{-1} + etomidate 0.3 mg kg^{-1}	5	35	60	0	30	70	5	35	60
Diazepam 0.125 mg kg^{-1} + etomidate 0.3 mg kg^{-1}	0	9	91	0	24	76	4	19	67
Fentanyl 1.25 μg kg^{-1} + thiopentone 3 mg kg^{-1}	5	40	55	0	25	75	0	40	60

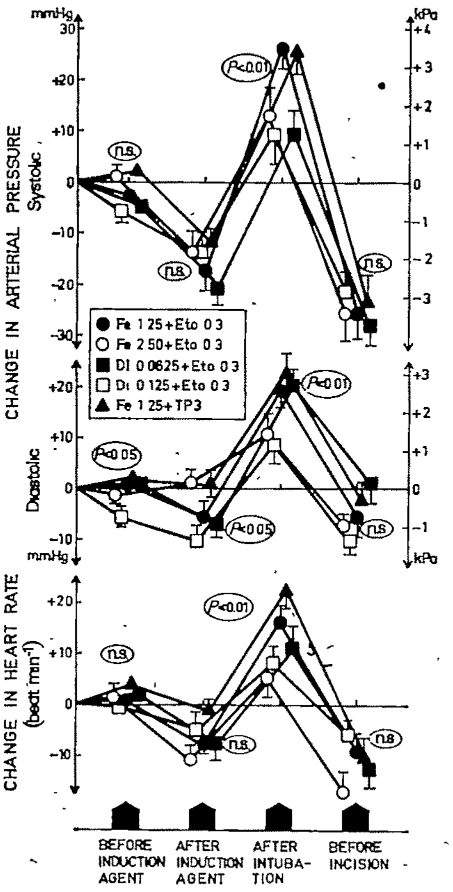

FIG. 1. Changes in systolic and diastolic arterial pressures and heart rate in premedicated patients during the induction of anaesthesia with etomidate 0.3 mg kg^{-1} preceded by i.v. fentanyl 1.25 μg kg^{-1} (●) or 2.5 μg kg^{-1} (○), or diazepam 0.0625 mg kg^{-1} (■) or 0.125 mg kg^{-1} (□); or induction with thiopentone 3 mg kg^{-1} preceded by i.v. fentanyl 1.25 μg kg^{-1} (▲). Encircled symbols indicate significances between groups according to an analysis of variance; n.s. = not significant.

involuntary muscle movements with etomidate; (3) awakening: delayed. Awakening was delayed and drowsiness in recovery room greatest in patients receiving diazepam 0.125 mg kg^{-1} before etomidate.

DISCUSSION

The use of fentanyl or diazepam before etomidate did not prevent pain during its injection or involuntary muscle movement, although these reactions were generally mild and the quality of induction broadly comparable to that of thiopentone. With these drug combinations, the changes in arterial pressure and heart rate after etomidate were similar to those after thiopentone.

Since an unacceptable high frequency of pain on injection and involuntary muscle movement has been noticed with etomidate alone (Holdcroft et al., 1976; Schuermans et al., 1978; Zacharias et al., 1978), this was not given. It has been suggested (Morgan, Lumley and Whitwam, 1975; Holdcroft et al., 1976; Ghoneim and Yamada, 1977; Zacharias et al., 1978) that etomidate 0.3 mg kg^{-1} would be sufficient for the induction of anaesthesia and approximately equivalent to thiopentone 3 mg kg^{-1}. However, our finding that 40% of the patients receiving thiopentone 3 mg kg^{-1} after fentanyl needed additional doses to induce sleep, compared with only 14% of the patients given etomidate 0.3 mg kg^{-1} after fentanyl, indicates that a 4-mg kg^{-1} dose of thiopentone might have been preferable.

The doses of fentanyl used were based on a recent recommendation by Doenicke (1978), and those of diazepam on the findings of Korttila and Linnoila (1975) and Korttila and others (1978).

Pain and involuntary muscle movements

When dissolved in water, etomidate caused pain on injection in 15% (Morgan, Lumley and Whitwam, 1975) to 50% (Zacharias et al., 1978) of patients. In propylene glycol solvent, pain occurred in 25–35% with excitatory phenomena in 85–95% of unpremedicated patients (Zacharias et al., 1978). Doenicke and colleagues (1973) noticed fewer muscle movements in healthy volunteers receiving diazepam 0.1 mg kg^{-1} i.v. before etomidate. In our study, the frequency of pain on injection (32–53%) occurred despite opiate–promethazine premedication and i.v. fentanyl or diazepam before the etomidate. Because patients were questioned as to whether they felt something unusual in their arms, rather than waiting for them to volunteer this information, the frequency of such a side-effect (severe in 5–20%) is likely to be greater than that reported by other workers.

Ghoneim and Yamada (1977) noticed a significant association between pain and movements, but Van Dijk (1978) and Zacharias and colleagues (1978) did not. In our study, movements were twice as frequent in patients with pain on injection than in those without pain, but the occurrence of movements during the administration of etomidate into a central vein suggests that pain on injection is not the only explanation for these excitatory phenomena.

Cardiovascular effects

Etomidate alone has been reported to have only minor haemodynamic effects (Brückner et al., 1974; Doenicke et al., 1974; Hempelmann et al., 1974; Patschke et al., 1977). The combination of etomidate with diazepam and fentanyl was associated with cardiovascular stability similar to that of thiopentone. An index of myocardial oxygen demand can be obtained by the product of the arterial pressure and heart rate (Robinson, 1967; Kaplan, Dunbar and Jones, 1976). If this rate/pressure product is used, it would appear that either fentanyl 0.2 mg or diazepam 5–10 mg given before etomidate may decrease the risks associated with the cardiovascular response to laryngoscopy and endotracheal intubation.

CONCLUSIONS

Pain on injection and excitatory phenomena were still unacceptably severe in 5% of the patients given i.v. fentanyl 2.5 $\mu g\ kg^{-1}$ or diazepam 0.125 $mg\ kg^{-1}$ before the administration of etomidate 0.3 $mg\ kg^{-1}$ for the induction of anaesthesia. Cardiovascular stability was of the same order with etomidate and thiopentone.

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COMPARAISON D'UNE COMBINAISON D'ETOMIDATE ET DE FENTANYL OU DE DIAZEPAM, ET DU THIOPENTONE EN TANT QU'AGENT D'INDUCTION POUR L'ANESTHESIE GENERALE

RESUME

Sur 104 malades prétraités devant subir une intervention chirurgicale générale, l'anesthésie a été provoquée soit par l'étomidate, à raison de 0,3 $mg\ kg^{-1}$, précédée par du fentanyl (1,25 ou 2,5 $\mu g\ kg^{-1}$, administré par voie intraveineuse) ou par du diazépam (0,0625 ou 0,125 $mg\ kg^{-1}$ aussi administré par voie intraveineuse) ou à l'aide de thiopentone précédé par du fentanyl (1,25 $\mu g\ kg^{-1}$ également administré par voie intraveineuse). En dépit de l'usage de fentanyl ou de diazépam, la fréquence de douleur au moment de l'injection, chez les malades recevant de l'étomidate, s'est située entre 32% et 53%, la douleur étant

particulièrement sévère dans 5–20% des cas. Aucune douleur n'a été ressentie par les patients recevant du thiopentone. La fréquence des mouvements involontaires s'est située entre 15 et 35% avec l'étomidate, et à 15% avec le thiopentone. La fréquence de la douleur tout comme celle des mouvements de muscles involontaires a été moindre lorsque le fentanyl à 2,5 μg kg^{-1} a précédé l'administration d'étomidate. Il n'y a eu aucune relation significative entre la douleur et le mouvement musculaire; trois malades sur 10 qui avaient reçu de l'étomidate dans une veine centrale ont eu de tels mouvements.

VERGLEICH ZWISCHEN ETOMIDAT, KOMBINIERT MIT FENTANYL ODER DIAZEPAM, MIT THIOPENTON ALS ALLGEMEINES NARKOSEEINLEITUNGSMITTEL

ZUSAMMENFASSUNG

Bei 104 vor der Operation vorbehandelten Patienten wurde die Narkose eingeleitet entweder mit 0,3 mg kg^{-1} Etomidat bei vorheriger Verabreichung von 1,25 oder 2,5 μg kg^{-1} Fentanyl oder 0,0625 oder 0,125 mg kg^{-1} Diazepam, beides intravenos, oder mit Thiopenton unter vorheriger Verabreichung von 1,25 μg kg^{-1} Fentanyl. Trotz Verwendung von Fentanyl oder Diazepam betrug die Häufigkeit von Schmerzen bei den Etomidat-Patienten bei der Injektion zwischen 32 und 53%—sehr stark bei 5–20% der Patienten. Bei Thiopenton-Patienten traten keine Schmerzen auf. Die Häufigkeit unwillkurlicher Bewegungen betrug 15–35% bei Etomidat und 15% bei Thiopenton. Die Häufigkeit von Scherzen und von unwillkürlichen Muskelbewegungen war am geringsten bei 2,5 μg kg^{-1} Fentanyl vor der Verabreichung von Etomidat. Zwischen Schmerzen und Muskelbewegungen bestanden keine offensichtlichen Beziehungen; drei von 10 Patienten, die Etomidat durch eine Hauptvene erheilten, zeigten solche Bewegungen.

COMPARACION DEL ETOMIDATO COMBINADO CON FENTANILO O DIAZEPAM, CON TIOPENTONA COMO AGENTE DE INDUCCION DE LA ANESTESIA GENERAL

SUMARIO

Se indujo la anestesia en 104 pacientes sometidos a premedicación antes de intervenciones quirúrgicas generales, ya sea con 0,3 mg kg^{-1} de etomidato precedido por 1,25 ó 2,5 μg kg^{-1} de fentanilo i.v. ó por 0,0625 ó 0,125 mg kg^{-1} de diazepan i.v., ya sea con tiopentona precedida por 1,25 μg kg^{-1} de fentanilo i.v. A pesar del uso del fentanilo o del diazepam, la frecuencia del dolor causado por la inyección en pacientes que recibían etomidato era entre 32% y 53%, siendo considerado como severo en 5–20% de los mismos. La tiopentona no causó ningún dolor a los pacientes. La frecuencia de movimientos involuntarios era del 15 al 35% con etomidato y del 15% con la tiopentona. La frecuencia tanto del dolor como de los movimientos involuntarios era menor al administrar 2,5 μg kg^{-1} de fentanilo antes de inyectar el etomidato. No hubo ninguna relación significativa entre el dolor y los movimientos musculares; tres de los 10 pacientes a quienes se administró etomidato en una vena central tuvieron estos movimientos.

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EFFECT OF PREMEDICATION ON ETOMIDATE ANAESTHESIA

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SUMMARY

The effect of premedication upon the induction of anaesthesia with etomidate was studied in 74 adult patients undergoing elective orthopaedic surgery. Premedication with fentanyl plus atropine or with diazepam plus atropine decreased the frequency of involuntary muscle movements without modifying the pattern of the circulatory effects of etomidate, although fentanyl increased the frequency of apnoea. Pain at the site of injection was not modified by premedication.

Etomidate is a recently-introduced water-soluble i.v. anaesthetic agent with minimal actions on the cardiovascular and respiratory systems (Doenicke et al., 1973; Kettler et al., 1974). However, the appearance of myoclonic movements and pain at the site of injection have been reported (Doenicke, 1974; Morgan, Lumley and Whitwam, 1975). This study was undertaken in order to explore the effects of premedication with diazepam plus atropine or with fentanyl plus atropine, on the induction of anaesthesia using etomidate as the induction agent.

PATIENTS AND METHODS

Seventy-four patients (age range 16–65 yr) undergoing elective orthopaedic surgery were studied. In all instances anaesthesia was induced with etomidate* 0.3 mg kg^{-1} injected over 45 s. The patients were allocated randomly to one of three groups: not pretreated ($n=26$); pretreated with fentanyl 10 $\mu g\ kg^{-1}$ i.v. plus atropine 10 $\mu g\ kg^{-1}$ i.v. ($n = 25$) or with diazepam 150 $\mu g\ kg^{-1}$ i.v. plus atropine 10 $\mu g\ kg^{-1}$ i.v. ($n = 23$) 10 min before the administration of the etomidate. All drugs were injected through an Abbocath 16 catheter inserted in an antecubital vein.

Direct arterial pressure, the electrocardiogram (e.c.g.), heart rate and respiratory rate were recorded continuously on a Greantbach 9232/1100 polygraph. Blood-gas tensions were measured in samples withdrawn through an arterial catheter 1 min before the administration of etomidate and 1 and 3 min thereafter. The time required to induce sleep was measured, and patients were observed for any evidence of pain, muscular movements, cough, hiccup or increased secretions occurring before the continuation of the anaesthetic with other agents. Complaints about pain were recorded, but no direct questions were asked about pain at the site of injection. Emetic sequalae after operation were not investigated.

RESULTS

Loss of consciousness was obtained 25–30 s after the administration of etomidate. No signs of excitation were observed in any patient before loss of consciousness. Eyelash and corneal reflexes were abolished consistently 2 min after termination of the injection. However, the laryngeal and pharyngeal reflexes were not affected in patients receiving etomidate without premedication.

The effects of etomidate on cardiovascular function and its modification by premedication are presented in table I. A slight increase of respiratory rate (lasting about 15–20 s) was detected immediately after the injection in about two-thirds of the unpremedicated patients. Apnoea of less than 15 s duration developed in two patients in this group and cough occurred in four additional patients. Patients premedicated with fentanyl plus atropine showed irregular patterns of breathing after the administration of etomidate. Premedication with diazepam plus atropine resulted in the development of apnoea in three of 23 patients, but in none did this last for more than 15 s. The frequency of apnoea, and the blood-gas tensions in the three groups of patients are presented in table II. Bicarbonate concentration and base excess values were not altered by etomidate.

Myoclonic movements were observed in 14 of 26 patients receiving etomidate alone. Three further patients in this group developed tonic movements.

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* Etomidate sulphate (0.2%) in a polyethyleneglycol vehicle.

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TABLE I. *Changes in arterial pressure and heart rate (mean ± SEM) after etomidate* 0.3 *mg kg*$^{-1}$. * $P < 0.05$; ** $P < 0.001$; *Student's t test of differences from initial values*

		Etomidate	Fentanyl + atropine + etomidate	Diazepam + atropine + etomidate
Systolic arterial pressure (mm Hg)	Before	138 ± 4.6	134 ± 2.7	133 ± 3.0
	After 1 min	122 ± 3.9*	115 ± 2.0**	110 ± 2.7**
	After 3 min	125 ± 5.0*	114 ± 2.5**	109 ± 3.3**
Diastolic arterial pressure (mm Hg)	Before	78 ± 2.6	81 ± 1.6	79 ± 1.6
	After 1 min	71 ± 2.6*	70 ± 1.9**	67 ± 1.7**
	After 3 min	72 ± 2.6	69 ± 2.0**	66 ± 1.9**
Heart rate (beat min^{-1})	Before	87 ± 2.3	107 ± 3.0	107 ± 3.4
	After 1 min	80 ± 2.7*	105 ± 2.6	107 ± 3.4
	After 3 min	89 ± 2.9	102 ± 2.3	104 ± 5.7

TABLE II. *Blood-gas tensions and oxygen saturation (mean ± SEM) and frequency of apnoea after administration of etomidate* 0.3 mg kg^{-1}. * $P < 0.05$; ** 0.001; *Student's t test of differences from initial values*

		Etomidate	Fentanyl + atropine + etomidate	Diazepam + atropine + etomidate
pH (unit)	Before	7.42 ± 0.007	7.40 ± 0.01	7.38 ± 0.005
	After 1 min	7.40 ± 0.005*	7.37 ± 0.01*	7.38 ± 0.008
	After 3 min	7.40 ± 0.007	7.37 ± 0.01*	7.37 ± 0.006
$P\text{co}_2$ (kPa)	Before	5.1 ± 0.11	4.3 ± 0.23	4.4 ± 0.2
	After 1 min	5.5 ± 0.09*	5.2 ± 0.13	4.9 ± 0.12
	After 3 min	5.5 ± 0.009*	5.3 ± 0.16	4.9 ± 0.11
$P\text{o}_2$ (kPa)	Before	10.9 ± 0.24	11.8 ± 0.55	11.5 ± 0.64
	After 1 min	9.2 ± 0.29**	8.3 ± 0.47**	9.0 ± 0.29**
	After 3 min	9.6 ± 0.31**	8.5 ± 0.47**	10.1 ± 0.4
Oxygen satn (%)	Before	95.0 ± 0.3	95.0 ± 1.1	95.0 ± 0.8
	After 1 min	93.0 ± 0.5**	85.0 ± 2.5**	91.0 ± 1.2*
	After 3 min	92.0 ± 0.5**	85.0 ± 2.5**	93.0 ± 0.8
Apnoeic periods (%)	Less than 30 s	2	3	3
	Lasting 30–60 s	—	3	—
	More than 60 s	—	4	—

Premedication with fentanyl and atropine reduced the appearance of involuntary movements after etomidate (six instances of myoclonic movements and one with tonic movements, of 25 patients). Similar results were obtained following premedication with diazepam and atropine (five patients with myoclonic and one with tonic movements; total of 23). Burning pain at the site of injection was reported spontaneously by about 20% of patients. This side-effect was recorded in five of 26 patients given no premedication, four of 25 receiving fentanyl, and six of 23 premedicated with diazepam. Marked salivation was observed in most patients receiving etomidate alone, but in none of those pretreated with atropine, plus either fentanyl or diazepam. Nausea during induction was recorded in three non-pretreated patients, in three pretreated with fentaynl and in one pretreated with diazepam. Vomiting was observed only in one fentanyl-pretreated patient.

DISCUSSION

The frequency of involuntary movements in the induction of anaesthesia with etomidate without sedative premedication has varied from about 18% (Macrez et al., 1976) to 59% (Rifat, Gamulin and Gemperlé, 1976) and even to more than 80% (Zacharias et al., 1978). This may be a result, in part, of the differences in the definition of myoclonia or to dosage or speed of injection, and also to the effects of movement of the patient during anaesthesia. In this study myoclonia was observed in 53% of patients receiving etomidate alone, but its frequency was decreased substantially by premedication with either diazepam or fentanyl. This is in accordance with the results of Ghoneim and Yamada (1977) and Zacharias and co-workers (1979).

The frequency of pain during the injection of etomidate was less in our series than in that of Ghoneim and Yamada (1977) and slightly less than in the series of Zacharias and co-workers (1978) in which polyethyleneglycol was used as a solvent. In contrast to the results of Kay (1976) and Zacharias and co-workers (1979) which showed a decrease in pain following premedication with fentanyl or pethidine, analgesic premedication did not influence pain on injection. A similar lack of influence was reported by Ghoneim and Yamada (1977). This discrepancy may be explained in part by differences in methods of evaluating pain or in the dosage of the analgesic drugs, and it is generally agreed that pain is less likely if etomidate is injected into a large vein.

The effects of etomidate on the circulatory and respiratory systems were only moderate when this drug was administered alone. The frequency of apnoea in our patients was of the order reported by Ghoneim and Yamada (1977) and less than in the series of Holdcroft and co-workers (1976), and was not influenced by the prior administration of diazepam. The highest frequency of apnoea was seen in fentanyl-premedicated patients. Since, in these patients, voluntary movements were less frequent than in those receiving etomidate alone, it is difficult to accept the contention (Morgan, Lumley and Whitwam, 1977) that involuntary movements play a major role in the induction of apnoea. Changes in blood-gas tensions were moderate and affected $P\mathrm{o}_2$ values mostly. They were more marked in patients premedicated with fentanyl and could be explained by changes in respiratory pattern.

The frequency of nausea and vomiting during the induction of anaesthesia with etomidate in this series is greater than in other reports (Macrez et al., 1976). However, nausea and vomiting after operation were not considered here since it was felt that these are related to the type of intervention and to the agent used for the maintenance of anaesthesia. If the problem of pain at the site of injection can be curtailed by use of an appropriate solvent or technique of administration, and if emetic emergence sequelae are shown to be in the range observed with other induction agents, etomidate, associated with a suitable premedication, may be a valuable i.v. anaesthetic in patients with cardiovascular or respiratory problems.

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EFFET DE LA PREMEDICATION SUR L'ANESTHESIE PAR L'ETOMIDATE

RESUME

L'effet de la prémédication sur l'induction de l'anesthésie par l'étomidate a été étudié sur 74 malades adultes, subissant une intervention chirugicale orthopédique à froid. La prémédication à base de fentanyl et d'atropine ou de diazépam et d'atropine a réduit la fréquence des mouvements musculaires involontaires sans modifier le mode des effets circulatoires, bien que le fentanyl ait augmenté

la fréquence de l'apnée. La douleur ressentie au point d'injection n'a pas été modifiée par la prémédication.

DIE WIRKUNG VON VORBEHANDLUNG AUF EINE ETOMIDAT-ANASTHESIE

ZUSAMMENFASSUNG

Diese Wirkung wurde bei 74 erwachsenen Patienten bei orthopädischen Operationen untersucht. Vorbehandlung mit Fentanyl plus Atropin oder mit Diazepam plus Atropin senkte die Häufigkeit unwillkürlicher Muskelbewegungen, ohne die Weise der Kreislaufeffekte von Etomidat zu modifizieren, obwohl Fentanyl die Häufigkeit von Apnoea erhohte. Schmerzen an der Injektionsstelle wurden durch die Vorbehandlung nicht modifiziert.

EFECTO DE LA PREMEDICACION EN LA ANESTESIA CON ETOMIDATO

SUMARIO

Se estudió el efecto de la premedicación sobre la inducción de la anestesia con etomidato en 74 pacientes adultos sometidos a operaciones quirúrgicas ortopédicas electivas. La premedicación con fentanilo adicionado de atropina o con diazepam adicionado de atropina hizo bajar la frecuencia de los movimientos musculares involuntarios sin modificar el tipo de efectos circulatorios del etomidato, aunque el fentanilo aumentara la frecuencia del apnea. La premedicación no alteró el dolor al punto de la inyección.

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EFFECTS OF KETAMINE ON THE PREGNANT UTERUS

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SUMMARY

Intra-uterine pressure was recorded by placing a Foley catheter in the extra-amniotic space before the termination of pregnancy in 25 patients, and Caesarean section in 12 patients. The effects of administration of i.v. ketamine 2 mg/kg body weight, sodium thiopentone 4 mg/kg body weight and ergometrine 0.5 mg, and intra-cervical 0.5% lignocaine 20 ml were measured in the first trimester of pregnancy, and i.v. ketamine and sodium thiopentone in late pregnancy. Ketamine was found to cause uterine contraction (mean increase 16.1 mm Hg) equal to ergometrine (mean increase 14.8 mm Hg) in early pregnancy, but exert no effect (mean decrease −1.33 mm Hg) in late pregnancy. Lignocaine in early pregnancy given as a paracervical block had no significant effect on intra-uterine pressure (mean increase 0.33 mm Hg). Sodium thiopentone (mean decrease −4.28 mm Hg first trimester and −2.22 mm Hg at term) in late pregnancy had no significant effect on intra-uterine pressure.

Ketamine hydrochloride (Ketalar) has been used widely in anaesthetic practice since the initial paper by Domino, Chodoff and Corssen (1965). In 1971 Galloon reported on its use as an induction agent for the termination of pregnancy by suction curettage, noting that blood loss was minimal during the procedure and that the uterus was well contracted at the conclusion of the operation. Later, Galloon (1973) measured the effect of ketamine on uterine muscle at hysterotomy and found an increase in both uterine tone and the intensity of contractility. Such effects had not been observed by Peltz and Sinclair (1973) on a pregnant uterus at term at Caesarean section, and thus it was decided to investigate further the action of ketamine and compare it with that of thiopentone in the first and last trimester of pregnancy and with ergometrine and lignocaine in early pregnancy.

PATIENTS AND METHODS

The procedure was explained to and informed consent obtained from 19 women undergoing therapeutic termination of pregnancy under general anaesthesia who were allocated randomly to three groups. The first group (I) received ketamine, the second (II) thiopentone and the third (III) ergometrine followed by ketamine. An oral premedication of lorazepam 3 mg and droperidol 5 mg was given 1 h before the induction of anaesthesia. A further six women (group IV) chose to have termination of pregnancy under local anaesthesia; no premedication was given to these patients.

In a second study, 12 women prepared for elective Caesarean section on account of cephalopelvic disproportion were allocated randomly to two groups. The first (group V) were given ketamine and the other (group VI) thiopentone for the induction of anaesthesia. In keeping with our routine practice for elective Caesarean section, the patients were not premedicated, and breathed 100% oxygen until the trachea was intubated. As soon as the intra-uterine pressure had been measured (*vide infra*) the patients were given suxamethonium i.v., an endotracheal tube was inserted and the lungs were ventilated in the normal manner. The anaesthetic was continued using conventional techniques and the intra-uterine catheter removed.

Before the induction of anaesthesia each patient was placed in the lithotomy position, the vulva and vagina were cleaned with chlorhexidine solution 0.5% and, after draping with sterile towels, a bivalve speculum was inserted into the vagina to display the cervix. A size 12 Foley catheter was fed through the cervix into the extra-amniotic space and the self-retaining balloon distended with 5 ml of saline. The catheter filled with saline was connected to a Bell and Howell transducer and the pressure recorded on a Devices recorder after calibration.

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TABLE I. *Mean changes (SEM) in intra-uterine pressure with drug administration*

	Termination of pregnancy					Caesarean section	
	Ketamine (Group I)	Thiopentone (Group II)	Ergometrine then ketamine (Group III)	(Total increase)	Lignocaine 0.5% (Group IV)	Ketamine (Group V)	Thiopentone (Group VI)
Resting pressure	11.1 (1.0)	15.6 (2.3)	8.8 (2.4)	23.6 (6.3)	11.7 (2.2)	15.2 (2.7)	22.0 (2.6)
Final pressure	26.4 (5.3)	11.3 (1.5)	23.6 (6.3)	34.8 (7.5)	12.0 (2.5)	13.8 (1.9)	19.8 (2.2)
Mean change	16.1 (4.9)	−4.3 (2.0)	14.8 (4.5)	26.0 (5.5)	0.3 (0.8)	−1.3 (1.5)	−2.2 (0.5)

Once a steady baseline pressure had been obtained for 3 min, ketamine 2 mg kg^{-1} body weight i.v. was given to groups I and V, thiopentone 4 mg kg^{-1} body weight i.v. to groups II and VI , and ergometrine 0.5 mg i.v. to group III. In group IV, lignocaine 0.5% 20 ml was injected in four divided doses at "12, 3, 6, and 9 o'clock" at the junction of the inner ⅔ and the outer ⅓ of the cervix. The intra-uterine pressure was recorded continuously until a steady state had been reached for a further 3 min. In group III ketamine 2 ml kg^{-1} body weight i.v. was administered and the recording of intra-uterine pressure continued until a new steady state had been obtained. The catheter was removed and the planned operation performed. No anaesthetic or surgical complications occurred. These was no case of post-abortion or puerperal infection.

The period of gestation at termination of pregnancy ranged from 8 to 12 week and at Caesarean section from 37 to 40 week. The *F* test was used to test for equality of variance before comparison of means. If the *F* test was positive, Student's *t* test was used; if not, a modified Student's *t* was applied.

RESULTS

The changes in intra-uterine pressure in the six groups are shown in figure 1 and the mean changes and SEM are listed in table I. The significance of the comparison of these means is detailed in table II. From these data it can be seen that the action of ketamine was quite different in early and in late pregnancy. In the first trimester it produced an increase in intra-uterine pressure comparable to that produced by ergometrine, whilst at term a decrease in intra-uterine tone was recorded, although this was not statistically significant. Thiopentone and lignocaine induced little change in intra-uterine pressure; the decrease noted in group II, although consistent, was not statistically significant.

Blood loss was measured at termination of pregnancy. The means for each group were 125, 150, 182 and 75 ml respectively. Because of inaccuracies inherent in estimations not employing a "washing machine" technique and the difficulties in allowing for fetal and liquor volume, these differences were not subjected to statistical analysis.

TABLE II. *Significance of comparison of changes in intra uterine pressure. TOP = Termination of pregnancy; l.s.c.s. = lower uterine Caesarean section; n.s. = not significant*

Groups	*t*	*P*
TOP Ketamine *v.* TOP thiopentone	3.57	< 0.01
TOP Ketamine *v.* ergometrine	1.77	n.s.
TOP Ketamine *v.* lignocaine	2.72	< 0.02
TOP Ketamine *v.* l.s.c.s. ketamine	2.94	< 0.02
TOP Thiopentone *v.* lignocaine	1.84	n.s.
TOP Thiopentone *v.* l.s.c.s. thiopentone	0.81	n.s.
TOP Thiopentone *v.* ergometrine	3.90	< 0.01
TOP Thiopentone *v.* ergometrine + ketamine	5.26	< 0.001
L.s.c.s. ketamine *v.* l.s.c.s. thiopentone	0.50	n.s.

No patient reported unpleasant dreams or exhibited disturbed behaviour patterns in the recovery period. This is in keeping with our experience when using lorazepam plus droperidol as a premedicant.

DISCUSSION

Simpson and colleagues (1974) reported no increase in peripheral oxytocin concentrations during the administration of ketamine, which suggests that its action is not mediated by oxytocin. Furthermore, they found that pharmacological concentrations of ketamine were not associated with contraction of the isolated pregnant uterine muscle strips, although these did respond to noradrenaline. In this study we found that, after a pressure plateau had been attained following the administration of ergometrine, there was a further, and equal, increase in intra-uterine pressure with the subsequent injection of ketamine. Therefore, uterine muscle was not stimulated maximally by ergometrine 0.5 mg and was capable of further contraction.

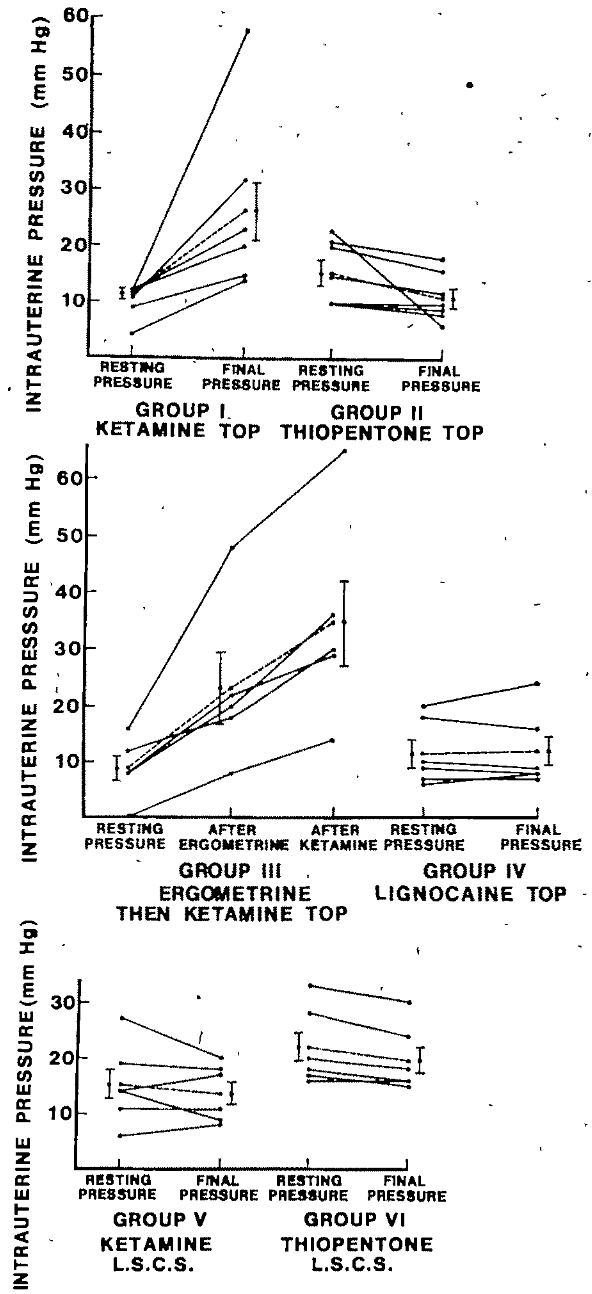

FIG. 1. Changes in intra-uterine pressure following drug administration. ●—— = individual patients; - - - - - = mean change; I = SEM; TOP = termination of pregnancy; L.s.c.s. = lower segment Caesarean section.

The response of the human myometrium to oxytocin changes markedly during pregnancy. It is resistant to its action except in very great concentrations until the onset of labour when there is a rapid increase in sensitivity (Theobald, Robards and Suter, 1969). The reaction of uterine muscle to ketamine is quite different, suggesting that this action is not mediated by oxytocin.

Unlike ketamine, prostaglandins E_2 and $F_2\alpha$ have a relatively uniform effect on uterine muscle throughout pregnancy. This would indicate that ketamine does not act directly through the release of prostaglandin or, if it does, its action is modified considerably by other hormonal changes.

Ketamine has been shown by Unni and Bovill (1972) to release both noradrenaline and adrenaline. Human myometrium contains α- and β-adrenergic receptors, the former being stimulatory and the latter inhibitory to uterine contraction. The fact that adrenergic nerve terminals decrease in number in late pregnancy (Klopper and Gardner 1973) could explain, at least in part, the decreased sensitivity of uterine muscle to ketamine in late pregnancy.

The contraction of the uterine muscle produced by ketamine in the first and probably second trimester (Galloon, 1973) is ideal from an operative point of view, as it enables safe curettage and decreases blood loss. The lack of response at term means that uterine blood flow and thus feto-placental exchange is not diminished.

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EFFETS DE LA KETAMINE SUR L'UTERUS GRAVIDE

RESUME

La pression intra-utérine a été enregistrée en plaçant un cathéter de Foley dans l'espace extra-amniotique, avant la fin de la grossesse de 25 personnes et avant de procéder à une opération césarienne sur 12 autres. Les effets de l'administration par voie i.v. de kétamine à raison de 2 mg par kg du poids du corps, de thiopentone de sodium à raison de 4 mg kg^{-1} et d'ergométrine sur la base de 0,5 mg, et de xylocaine 20 ml à 0,5% par voie intra-cervicale ont été mesurés au cours du premier trimestre de la grossesse. Les effets de la kétamine et du thiopentone de sodium administrés par voie i.v. ont été évalués vers la fin de la grossesse. On a trouvé que la kétamine produisait des contractions utérines au début de la grossesse (augmentation moyenne de 16,1 mm Hg) égales à celles produites par l'ergométrine (augmentation moyenne 14,8 mm Hg), mais n'avait aucun effet vers la fin de la grossesse (diminution moyenne −1,33 mm Hg). La xylocaïne administrée comme blocage paracervical en début de grossesse n'avait aucun effet significatif sur la pression intra-utérine (augmentation moyenne 0,33 mm Hg). Le thiopentone de sodium administré en fin de grossesse n'a eu aucun effet significatif sur la pression intra-utérine (diminution moyenne −4,28 mm Hg lors du premier trimestre de grossesse et −2,22 mm Hg à terme).

WIRKUNGEN VON KETAMIN AUF DEN SCHWANGEREN UTERUS

ZUSAMMENFASSUNG

Intrauteriner Druck wurde durch Einführung eines Foley-Katheters in den äusseren Amnionraum von 25 Patientinnen unmittelbar vor der Schwangerschaftsunterbrechung eingefuhrt, und bei 12 Patientinnen mit Kaiserschnitt. Die Wirkungen von 2 mg kg^{-1} Körpergewicht Ketamin intravenos, von 0,5 mg Ergometrin und von 0.5% Xylocain 20 ml, intrazervikal wurden im ersten Trimester der Schwangerschaft gemessen, die von intravenosem ketamin und sodium thiopenton bei späteren Schwangerschaftsstadien. Ketamin bewirkte Uteruskontraktion (mittlerer Anstieg 16,1 mm Hg) gleich wie ergometrin (mittlerer Anstieg 14,8 mm Hg) in der frühen Schwangerschaft, hatte aber keine Wirkung (mittlerer Abstieg 1,33 mm Hg) in der späteren Schwangerschaft. Als parazervikale Blockierung bei früher Schwangerschaft verabreichtes Xylocain hatte keine Auswirkung auf den intrauterinen Druck (mittlerer Anstieg 0,33 mm Hg). Sodium thiopenton (mittlerer Abstieg −4,28 mm Hg erstes Trimester und −2,22 mm Hg spater) hatte in der späteren Schwangerschaft ebenfalls keinen wesentlichen Einfluss auf den intrauterinen Druck.

EFECTOS DE LA QUETAMINA SOBRE EL UTERO EMBARAZADO

SUMARIO

Se registró la presión intra-uterina en 25 pacientes antes del término del embarazo y en 12 pacientes antes de la operación cesárea, al colocarles una sonda de Foley en el espacio extra-amniótico. Los efectos de la administración i.v. de 2 mg kg^{-1} peso corporal de quetamina, de 4 mg kg^{-1} peso corporal de tiopentona sódica y de 0,5 mg de ergometrina, así como de xilocaina al 0,5% 20 ml intra-cervical fueron medidos en el primer trimestre del embarazo, y los de la quetamina y tiopentona sódica i.v. en la última parte del mismo. Se estableció que la quetamina ocasionaba contracciones uterinas (aumento medio 16,1 mm Hg) iguales a las de la ergometrina (aumento medio 14,8 mm Hg) en la primera parte del embarazo, pero no tenía ningún efecto (aumento medio −1,33 mm Hg) en la última parte del mismo. La xilocaina administrada como bloque paracervical en la primera parte del embarazo no tenía efectos significativos algunos en la presión intra-uterina (aumento medio 0,33 mm Hg). La tiopentona sódica (aumento medio −4,28 mm Hg en el primer trimestre y −2,22 mm Hg al término) no tenía ningún efecto significativo en la presión intra-uterina en la última parte del embarazo.

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KETAMINE INFUSIONS: PHARMACOKINETICS AND CLINICAL EFFECTS

J. Idvall, I. Ahlgren, K. F. Aronsen and P. Stenberg

SUMMARY

The clinical effects and pharmacokinetics of ketamine, administered as an i.v. infusion, were studied in 31 patients. Anaesthesia was induced with ketamine 2 mg kg^{-1} i.v. and maintained using an i.v. infusion of ketamine, supplemented by nitrous oxide. The plasma concentrations of ketamine, nor-ketamine and dehydro-nor-ketamine were analysed using gas–liquid chromatography. The average maintenance dose of ketamine was 41 ± 21 μg kg^{-1} min^{-1}, but there was an obvious decrease in the dose required as anaesthesia progressed. This dose gave a stable plasma concentration of ketamine of 9.3 ± 0.8 μmol $litre^{-1}$. Patients recovered at 2.7 ± 0.9 μmol $litre^{-1}$. Plasma half-life of ketamine was 79 ± 8 min. Maximum concentration of nor-ketamine was 4.7 ± 2.4 μmol $litre^{-1}$ and of dehydro-nor-ketamine 3.2 ± 1.9 μmol $litre^{-1}$. There were transient increases (15–30% of pre anaesthetic values) in arterial pressure, heart rate and cardiac output during operation. No post-operative respiratory depression was seen.

Ketamine has been acclaimed on account of its safety and its favourable effects upon the cardiovascular and respiratory systems (Langrehr et al., 1967; Lanning and Harmel, 1975) and, because of its sympathomimetic and antiarhythmic properties, it is useful in poor-risk and hypovolaemic patients. Over the years several anaesthetic techniques have been studied and many different supplementary drugs have been administered with ketamine. For example, a continuous infusion technique has been recommended to decrease the total dose and to obtain smoother anaesthesia. This study was undertaken to evaluate further the pharmacokinetic properties and clinical effects of a continuous infusion of ketamine supplemented with nitrous oxide.

PATIENTS AND METHODS

Patients

Fifteen male and 16 female patients undergoing major abdominal surgery were studied. The mean age was 67 yr (SD 15) (range 24–90 yr) and mean body weight 66.5 kg ± 14.3 (range 32–100 kg). The patients were classified according to the grading of physical status of the American Society of Anesthesiologists (ASA) described by Saklad (1941); two patients were grade I, five grade II, 15 grade III and nine grade IV.

All patients had normal serum creatinine concentrations. Seven were jaundiced because of extrahepatic obstruction. None of the patients in the study had a history of psychiatric disease or abuse of alcohol. Mean operation time was 159 ± 63 min.

Cardiac output was determined in six male and four female patients selected at random, mean age 68 ± 7 yr, mean ASA grade III.

To evaluate the effect of ketamine on respiration, the patients were divided into two groups with respect to premedication: group 1 (15 patients) received atropine only and group 2 (16 patients) atropine and pethidine hydrochloride or fentanyl. The mean age and ASA grade were greater in group 1.

Anaesthetic technique

Atropine 0.5 mg i.m. was given as premedication in all patients. Fourteen patients received also pethidine (Petidin, ACO) 50–75 mg and promethazine (Lergigan, Recip) 25 mg i.m. and two patients received a mixture of fentanyl 0.1 mg and droperidol 5 mg i.m. (Leptanal comp., Leo) as well as atropine.

The induction dose of ketamine (2 mg/kg body weight i.v.) was given over a period of 1 min (Ketalar 10 mg ml^{-1}, Parke–Davis). The trachea was intubated under paralysis induced with suxamethonium (Celocurin-klorid, Vitrum) 75–100 mg i.v.

The lungs were ventilated artificially using a Servo-Ventilator (Elema–Schönander, Stockholm) set to deliver 65% nitrous oxide in oxygen. Adequate

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ventilation was verified by the analysis of arterial blood-gas tensions. After the induction of anaesthesia, a continuous i.v. infusion of ketamine 50 mg ml^{-1} was started via a cubital vein using a Dascon infusion pump model 300, allowing flows from 0.01 to 9.99 ml h^{-1}. The initial infusion rate was 40 $\mu g\ kg^{-1}\ min^{-1}$, and was adjusted to maintain sleep and produce adequate operating conditions. During the operation neuro-muscular blockade was maintained with the intermittent administration of suxamethonium or pancuronium (Pavulon, Organon). The ketamine infusion was discontinued 10–20 min before the end of the operation. All patients had 2 min of pure oxygen-breathing before removal of the tracheal tube.

Clinical observations

After the anaesthetic, recovery was considered acceptable if the patient could state his name and date of birth. In the ward after operation the patients were assessed continually with emphasis on general behaviour, alertness and the onset of pain. Two hours after anaesthesia and on the following day all patients were interviewed by a nurse anaesthetist about the anaesthetic, being questioned especially about dreaming. In this study only two nurses took part in the anaesthetic procedures and the interviews.

Monitoring of cardiovascular and respiratory function

Arterial pressure was monitored directly via a catheter which was inserted to a radial artery before anaesthesia (transducer EMT 746, Elema-Schönander, Stockholm). E.c.g. was recorded continuously. Cardiac output was determined according to Wassén (1956). All measurements were made before the induction of anaesthesia, 5–15 min after induction and during steady-state anaesthesia. Arterial blood-gas tensions and pH were measured just before anaesthesia (after premedication), during the operation, and 2 h afterwards (IL 413, Instrumentation Laboratories, Boston).

Analysis of ketamine and its metabolites

The gas–liquid chromatographic technique of Chang and Glazko (1972) was used.

Chemicals. Ketamine hydrochloride (2-(o-chlorophenyl)-2-(methylamino) cyclohexanone hydrochloride), metabolite I (2-amino-2-(o-chlorophenyl) cyclohexanone hydrochloride), metabolite II (2-amino-2-(o-chlorophenyl)-3-cyclohexen-1-one hydrochloride) and internal standard (2-(o-bromophenyl)-2-(methylamino) cyclohexanone hydrocholride) were supplied by Parke–Davis. Benzene (Merck 1785), anhydrous sodium sulphate (Merck 6649), heptafluorobutyric anhydride (Pierce 63163) and pyridine (Merck 7463) were used without further purification.

Apparatus. A Varian 3700 Gas Chromatograph equipped with a nickel-63 electron capture detector and a glass column (150 × 0.2 cm i.d.) packed with 3% OV-17 on GasChrom Q 80/100 mesh were used for the analyses. Injection temperature was maintained at 220 °C, column temperature at 205 °C and the detector at 250 °C. Nitrogen 30 ml min^{-1} was used as the carrier gas.

Procedure. Samples of arterial blood were taken into heparinized tubes 5 and 20 min after the induction of anaesthesia, every 20 min during the steady state and 15, 30, 45, 60 and 120 min after stopping the infusion. A few samples were collected 24 h after anaesthesia. The tubes were centrifuged at 1000 *g* for 10 min, and the plasma was then stored at −20 °C before analysis (maximum storage time 2 months).

Statistics

The Wilcoxon test for paired observations or the Mann–Whitney test for comparison of groups were used for statistical calculations.

RESULTS

The anaesthetic technique described gave good operating conditions in all patients. Recovery was rapid; 15 patients were able to state their names and date-of-birth within 5–10 min of extubation, 13 patients showed the same degree of alertness within 30 min, and two patients within 60 min. None reported awareness or dreams during the operation, but four patients experienced dreams in the period after operation and in two of these, aged 24 and 37 yr, the dreams were unpleasant. Otherwise, no excitement, agitation, anxiety or involuntary motor activity occurred during recovery. Nausea and vomiting were noted in three patients. Directly after the operation one patient complained of pain, which was abolished by diazepam 5 mg i.v. No other patient required an analgesic or sedative during the first 2 h after operation.

Changes in systolic and diastolic arterial pressure and heart rate are shown as per cent of pre-anaesthetic value in figure 1. There was an initial increase in all values, and the peak value was reached within 10 min of the induction of anaesthesia. The maximum mean increase in systolic pressure was 31%, in diastolic pressure 27% and in heart rate 19%. About 30 min after induction arterial pressure and heart rate

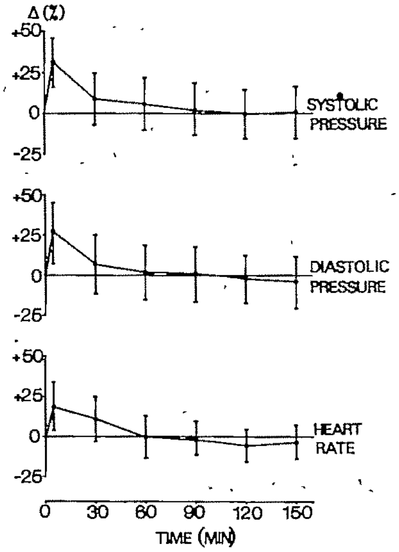

FIG. 1. Percentage change in systolic and diastolic arterial pressures and heart rate from initial values in all patients ($n = 31$) expressed as mean ± SD.

returned gradually to the original values where they remained throughout the remainder of the anaesthetic.

The calculated cardiac index and stroke index are shown in table I. Five to 15 min after the induction of anaesthesia cardiac index had increased significantly ($P < 0.05$) from 3.1 litre min^{-1} m^{-2} to 3.5 litre min^{-1} m^{-2}. Later, during steady-state anaesthesia, cardiac index decreased to 2.6 litre min^{-1} m^{-2} ($P < 0.01$). There were no significant changes in stroke index.

TABLE I. *Changes in cardiac index and stroke index in 10 patients. Mean ± SD. P value refers to comparison with values before anaesthesia*

	Before anaesthesia	5–15 min after induction of anaesthesia	During steady-state anaesthesia
Cardiac index (litre min^{-1} m^{-2})	3.1 ± 0.8	3.5 ± 0.7 ($P < 0.05$)	2.6 ± 0.6 ($P < 0.01$)
Stroke index (ml $beat^{-1}$ m^{-2})	34.0 ± 9.0	34.0 ± 10 (n.s.)	31.0 ± 10 (n.s.)

Frequent ventricular arrhythmia was noted before operation in three patients, but this decreased or disappeared during ketamine anaesthesia.

Although Pa_{CO_2} and pH were unchanged after operation, mean Pa_{O_2} increased in the period after operation ($P < 0.02$). Pa_{O_2} values studied separately in the two subgroups revealed no significant change in group 1, but a significant increase in group 2 ($P < 0.01$) (table II).

TABLE II. *Arterial blood-gas tensions in all patients ($n = 31$) before and after ketamine anaesthesia and Pa_{O_2} of the patients when divided into two groups. Group 1 ($n = 15$) premedicated with atropine only and group 2 ($n = 16$) with atropine and an analgesic (pethidine or fentanyl). Mean ± SD*

	Before operation	After operation	P
Pa_{CO_2} (kPa) ($n = 31$)	5.0 ± 0.4	5.0 ± 0.5	n.s.
Pa_{O_2} (kPa) ($n = 31$)	10.0 ± 1.3	11.0 ± 1.5	< 0.02
Pa_{O_2} (kPa)			
Group 1 ($n = 15$)	10.2 ± 1.4	10.4 ± 1.5	n.s.
Group 2 ($n = 16$)	10.0 ± 1.3	11.2 ± 1.3	< 0.01

The mean plasma concentrations of ketamine and metabolites I and II are shown in figures 2 and 3. Five minutes after the injection of the initial loading dose, a plasma concentration of ketamine of about 60 µmol $litre^{-1}$ was found. The plasma concentration of ketamine then decreased rapidly to about 7–10 µmol $litre^{-1}$ where it remained throughout the anaesthetic. Mean infusion rate for the total time of anaesthesia was 41 ± 21 µg kg^{-1} min^{-1}. During the first 30 min of the operation the ketamine infusion rate was 58 ± 22 µg kg^{-1} min^{-1} and during the last 30 min it was 17 ± 17 µg kg^{-1} min^{-1}. After the infusion was stopped, the plasma ketamine concentration decreased during the distribution phase, which lasted about 30 min. This phase was followed by an elimination phase with the ketamine concentration

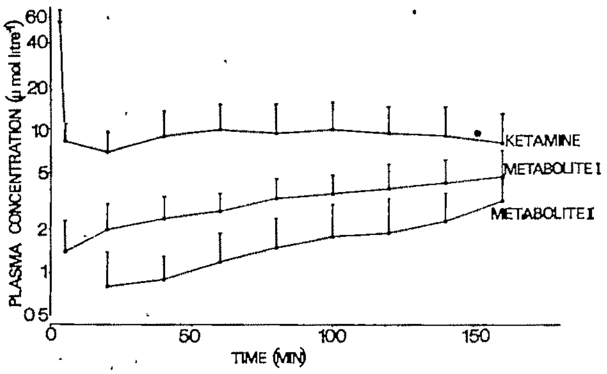

FIG. 2. Plasma concentrations of ketamine, nor-ketamine (metabolite I) and dehydro-nor-ketamine (metabolite II) during anaesthesia. Mean + SD. All anaesthetics ⩾ 150 min.

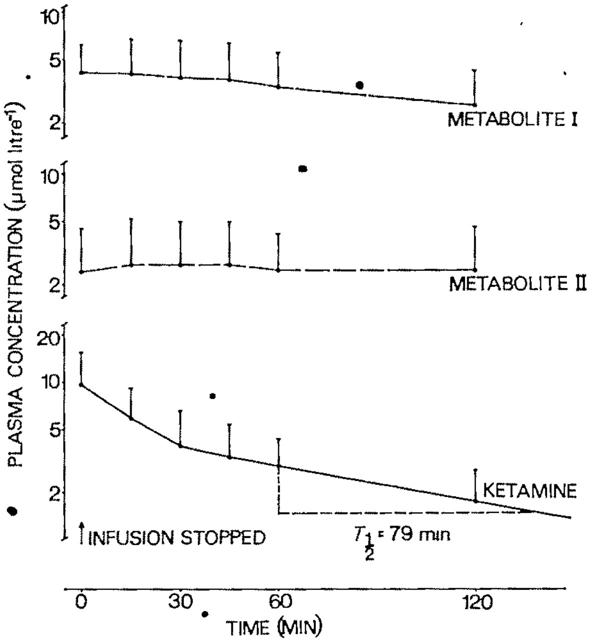

FIG. 3. Plasma concentrations of ketamine, nor-ketamine (metabolite I) and dehydro-nor-ketamine (metabolite II) during the distribution and elimination phases. Mean +SD.

decreasing at a slower rate. Plasma half-life of ketamine was calculated to be 79 ± 8 min.

Of the two metabolites, metabolite I was present as early as 5 min after the injection of the loading dose. Metabolite II appeared in significant amounts in the 20-min sample. During the elimination phase, both metabolites were present at greater concentrations than that of ketamine.

The anaesthetic plasma concentration of ketamine, calculated as the mean of the ketamine concentrations during steady-state anaesthesia, was 9.3 ± 0.8 µmol litre^{-1}, while the plasma concentration during recovery was 2.7 ± 0.9 µmol litre^{-1}.

Maximal concentrations of metabolite I (4.7 ± 2.4 µmol litre^{-1} and metabolite II (3.2 ± 1.9 µmol litre^{-1}) were observed about 3 h after the induction of anaesthesia. Analysis of a few samples drawn 24 h after the operation revealed measurable plasma concentrations of metabolite II while ketamine and metabolite I were not detected.

DISCUSSION

Ketamine produced good surgical anaesthesia and total amnesia. In addition, however, a neuromuscular blocking drug was necessary for intra-abdominal surgery, as has been observed previously by Gjessing (1968).

Different techniques of anaesthesia have been tried in order to minimize the side-effects of ketamine, especially its psychotomimetic effects. Sedative drugs as premedication, as supplementation during anaesthesia or as postoperative sedation have been used to decrease the frequency of emergence phenomena. Diazepam (Kothary and Zsigmond, 1975), lorazepam (Dundee and Lilburn, 1978) and droperidol (Sadove et al., 1971) have been used for this purpose, but according to Lo and Cumming (1975) ketamine-induced sleep time and ketamine plasma half-life were prolonged in patients premedicated with diazepam, hydroxyzine or secobarbitone. Therefore, in this study, a sedation technique was avoided as a rapid recovery was considered important.

A decrease in the dose of ketamine has been suggested as a means of reducing sequelae (Chodoff and Stella, 1966) and this can be achieved by the use of a continuous infusion for the maintenance of anaesthesia (Sabathie et al., 1976; El-Naggar et al., 1977; Hatano, Nishiwada and Matsumura, 1978; Lilburn, Dundee and Moore, 1978). The use of nitrous oxide as a supplement has been shown by Wessels, Allen and Slogoff (1973) to reduce the dose of ketamine and ketamine-dependent side-effects.

In this study, in which ketamine was given by continuous infusion with nitrous oxide as a supplement, recovery was fast and psychotomimetic side-effects were not prominent. Like Garfield and colleagues (1972), we found early verbal and tactile stimulation during the recovery period beneficial.

Using this technique of anaesthesia, a stable concentration of ketamine in the plasma was achieved. None of the patients had received drugs that might have interfered with the metabolism of ketamine or its metabolites. This is reflected in the small differences in metabolic pattern between patients. However, the relationship between the dose required and body weight was not good, a standard deviation of about 50% being obtained. Wulfsohn (1972) has reported that lean body mass is a better basis on which to calculate the dose of ketamine required for induction, and this may be true also for the maintenance dose. Moreover, it was found that the maintenance dose could be decreased gradually during the operation, the dose during the last 30 min being significantly less than that during the first 30 min. This agrees with a two-compartment model of pharmacokinetics with re-entry of ketamine from the peripheral to the central compartment. Lilburn, Dundee and Moore (1978) found that the amount of ketamine per unit time could be decreased for long operations. With ketamine alone, they administered about 100–200 $\mu g\ kg^{-1}\ min^{-1}$, the dose required being smaller with controlled than with spontaneous ventilation. In this study the maintenance dose was less because of supplementary nitrous oxide and the larger loading dose, 2 $mg\ kg^{-1}$ instead of 1 $mg\ kg^{-1}$. If the initial loading dose is insufficient, anaesthetic concentrations will be attained slowly and an increased rate of infusion will be required. This will lead to greater total ketamine dosage, greater loading of tissue stores and delayed recovery after anaesthesia.

In this study metabolite I was the major metabolite noted during anaesthesia, metabolite II reaching a plasma concentration approximately equal to that of metabolite I about 2 h after the infusion was stopped. Analysis of the samples drawn 24 h after anaesthesia showed that metabolite II was the major metabolite at that time. The metabolites appeared to have no significant anaesthetic properties.

Despite liver insufficiency in seven of the patients no significant differences were seen in the metabolism of ketamine in these patients as compared with the other patients. Nor were there any differences in the dose required. This is in agreement with the results of Schaps and Hauenschild (1977).

The haemodynamic study confirmed that ketamine is a circulatory stimulant. Our results are compatible with those of Virtue and colleagues (1967) who studied healthy volunteers, and with the results of Lorhan and Lippman (1971), who studied elderly poor-risk patients. The stimulatory effect could depend on an increase in sympathetic activity, which has been demonstrated by Traber, Wilson and Priano (1968) and Zsigmond, Kelsch and Kothary (1975). Moreover, ketamine has been shown to display a vagolytic action, which can be attenuated by atropine (Traber, Wilson and Priano, 1970). Thus the stimulatory effect observed in this study was modified by atropine, given to all the patients as premedication. Lilburn, Dundee and Moore (1978) found in their study that the combination of ketamine and pancuronium produced an unacceptable degree of hypertension and tachycardia. However, such effects were not observed in this study.

Cardiac index had increased 5–15 min after the induction of anaesthesia ($P < 0.05$), a change which coincided with the maximum increases in arterial pressure and heart rate, but there was no change in stroke index—results which are in agreement with those of Tweed, Minuck and Mymin (1972).

The antiarrhythmic effect observed in this study is similar to that noted by Dowdy and Kaya (1968) who found a significant prolongation of the functional refractory period after the administration of ketamine to dogs with ventricular disrhythmia.

Analysis of arterial blood-gas tensions revealed no respiratory depression after operation when compared with the preoperative values, similar to those observed by Virtue and colleagues (1967). A significant increase in postoperative Pa_{O_2} was observed in the patients in group 2. The most likely explanation for this is that the pre-operative blood sample was taken when the patients were under the influence of premedication with pethidine or fentanyl and had, consequently, some depression of respiration (Eckenhoff and Helrich, 1958; Downes, Kemp and Lambertsen, 1967; Goodman and Gilman, 1970).

In this study, ketamine, given by a continuous infusion in combination with nitrous oxide, was found to produce favourable haemodynamic conditions, no respiratory depression after operation and few psychotomimetic side-effects. It may be concluded that ketamine given in this manner along with a neuromuscular blocking drug is a suitable anaesthetic technique for intra-abdominal surgery, particularly in elderly patients.

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INFUSIONS DE KETAMINE: PHARMACOCINETIQUE ET EFFETS CLINIQUES

RESUME

On a étudié les effets cliniques et la pharmacocinétique de la kétamine sur 31 malades auxquels on avait injecté ce produit par voie intraveineuse. L'anesthésie a été produite par la kétamine administrée par voie intraveineuse à raison de 2 mg kg^{-1} et elle a été maintenue à l'aide d'une injection intraveineuse de kétamine, complétée par du protoxyde d'azote. Les concentrations de kétamine, de nor-kétamine et de déshydro-nor-kétamine dans le plasma ont été analysées par chromatographie en phase gazeuse–liquide. La dose moyenne de kétamine d'entretien a été de 41 ± 21 μg kg^{-1} min^{-1}, mais il y a eu une diminution évidente dans la dose requise, au fur et à mesure que l'anesthésie a progressé. Cette dose a donné une concentration stable de kétamine dans le plasma de 9,3 ± 0,8 μmol litre^{-1}. Les patients ont repris conscience à 2,7 ± 0,9 μmol litre^{-1}. La demi-vie de la kétamine dans le plasma a été de 79 ± 8 min. La concentration maximale de nor-kétamine a été de 4,7 ± 2,4 μmol litre^{-1} et celle de déshydro-nor-kétamine de 3,2 ± 1,9 μmol litre^{-1}. Il y a eu des augmentations transitoires (15–30% des valeurs pré-anesthésie) de la pression artérielle, de la fréquence cardiaque et du débit cardiaque pendant l'opération. On n'a constaté aucune dépression respiratoire postopératoire.

KETAMIN-INFUSIONEN: PHARMAKOKINETISCHE UND KLINISCHE WIRKUNGEN

ZUSAMMENFASSUNG

Die pharmakokinetischen und klinischen Wirkungen einer intravenos verabreichten Ketamin-Infusion wurden bei 31 Patienten studiert. Narkose wurde durch 2 mg kg^{-1} Ketamin intravenos eingeleitet und durch eine intravenose Infusion von Ketamin, ergänzt durch Stickoxyd, aufrecht erhalten. Die Plasmakonzentrationen von Ketamin, Norketamin und Dehydronorketamin wurden bei einer Gas-Flussigkeitschromatographie analysiert. Die mittlere Aufrechterhaltungsdosis von Ketamin betrug 41 ± 21 μg kg^{-1} min^{-1} doch kam es zu einem offensichtlichen Sinken der erforderlichen Dosis bei fortschreitender Narkose. Diese Dosis ergab eine stabile Plasmakonzentration von 9,3 ± 0,8 μmol Liter^{-1} Ketamin. Patienten erholten sich bei 2,7 ± 0,9 μmol Liter^{-1}. Die Plasma-Halbwertzeit von Ketamin betrug 79 ± 8 min. Die Maximalkonzentration von Norketamin betrug 4,7 ± 2,4 μmol Liter^{-1}, und von

Dehydronorketamin 3,2 ± 1,9 μmol Liter^{-1}. Es gab vorübergehende Anstiege (15–30% der Vornarkosewerte) von arteriellem Druck, Herzminutenvolumen und Herztätigkeit während der Operation. Eine postoperative respiratorische Dämpfung wurde nicht beobachtet.

INFUSIONES DE QUETAMINA: EFECTOS FARMACOCINETICOS Y CLINICOS

SUMARIO

En 31 pacientes, se estudió los efectos clínicos y farmacocinéticos de la quetamina administrada como infusión i.v. Se indujo la anestesia con 2 mg kg^{-1} de quetamina y fue mantenida por medio de una infusión i.v. de quetamina, complementada por óxido nitroso. Se analizaron las concentraciones en el plasma de quetamina, nor-quetamina y dehidro-nor-quetamina mediante cromatografía gas-líquido. La dosis media de mantenimiento de quetamina era de 41 ± 21 μg kg^{-1} min^{-1}, pero hubo una disminución evidente de la dosis necesaria a medida que progresara la anestesia. Esta dosis dió una concentración estable de quetamina en el plasma de 9,3 ± 0,8 μmol litro^{-1}. Los pacientes se recuperaron en 2,7 ± 0,9 μmol litro^{-1}. La media-vida de la quetamina en el plasma fue de 79 ± 8 min. La concentración máxima de nor-quetamina fue de 4,7 ± 2,4 μmol litro^{-1} y de dehidro-nor-quetamina de 3,2 ± 1,9 μmol litro^{-1}. Durante la operación, hubo aumentos transitorios (15–30% de los valores pre-anestéticos) en la presión arterial, el ritmo cárdiaco y la función sistólica. No se registró ninguna depresión respiratoria post-operatoria.

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PLASMA VISCOSITY AND CREMOPHOR-CONTAINING ANAESTHETICS

L. GRAMSTAD AND J. STOVNER

SUMMARY

The cremophor-containing anaesthetic agents, Althesin, propanidid and diazepam, were added to plasma *in vitro* and administered to patients. *In vitro* these anaesthetics, and cremophor alone in concentrations equal to those obtained *in vivo*, decreased the viscosity of plasma 45% at shear rate 11.5 s^{-1}. In 11 patients given cremophor-containing anaesthetics to induce anaesthesia, plasma samples obtained 5 min after injection showed a mean decrease in viscosity of 42% compared with the pre-induction values. The effect on viscosity after a single dose disappeared in 50 min. Triton x-100 added to plasma caused a decrease in viscosity similar to that of cremophor. The interaction *in vitro* of cremophor and Triton x-100 with concentrated urea was found to be identical both in plasma and dextran. This suggests that cremophor acts by increasing the sheet of structured water around the protein molecules, thereby preventing the aggregation of proteins.

During the induction of anaesthesia it was observed that the flow of blood from a plastic cannula in a cubital vein increased considerably after the administration of a certain group of anaesthetic agents. The agents involved were propanidid (Epontol, Bayer), alphaxalone/alphadolone (Althesin, Glaxo) and diazepam (Stesolid MR, Dumex) all of which are dissolved in 20% polyoxyethylated castor oil, marketed as Cremophor EL (BASF, Ludwigshaven). We report on the effects of these anaesthetics on the viscosity of plasma both *in vitro* and after injection to patients. A possible mechanism of action was investigated by studying the interaction of both cremophor and Triton x-100 with concentrated urea on the viscosity of both plasma and dextran 70.

Viscosity is a measure of the internal friction of a liquid expressed as the ratio between the friction force or shear stress, and the velocity of movement, or shear rate (Gordon and Ravin, 1978). Ideal Newtonian liquids like water or alcohol have a constant viscosity because in such liquids the molecular friction varies in proportion to the velocity. Plasma, on the other hand, is a mixture of protein molecules which aggregate in slow motion causing the viscosity to increase. Therefore, in the present experiments we have chosen to determine plasma viscosity at five different shear rates.

METHODS

In vivo *studies*

Patients. Twenty-nine apparently healthy women aged between 20 and 32 yr were studied. All were to undergo dilatation and curettage as part of the investigation of and treatment for infertility.

Premedication consisted of atropine 0.5 mg and ketobemidone 5 mg given i.m. 1 h before operation. Anaesthesia consisted of diazepam 5 or 10 mg i.v. (given as the cremophor-containing Stesolid MR) followed by propanidid 1 ml per 10 kg, or Althesin 0.5 ml per 10 kg body weight. In addition, nitrous oxide in oxygen (3 : 2) was given. As all the three anaesthetic agents contain cremophor in a concentration of 20%, the total volume given to each patient was an indication of the plasma concentration of cremophor.

The first blood sample was taken in the operating theatre shortly before the induction of anaesthesia, simultaneously with the insertion of a plastic cannula in a cubital vein. Further samples were taken from the same cannula at 5, 10, 20, 30, 40 and 50 min after induction. About 5 ml of blood was collected each time in an EDTA-containing tube (Vacutainer No. 3202 QS) ensuring thorough mixing with the EDTA. After centrifugation the plasma was kept at 4 °C until the determinations of viscosity were performed.

Plasma viscosity determinations were performed with a Wells-Brookfield cone-plate microviscometer, thermically controlled at 37 °C. Plasma samples of

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1.8 ml were used. Readings were taken every minute at five different shear rates (230, 115, 46, 23 and 11.5 s^{-1}). The mean value of four consecutive readings was used in the calculations. The viscosity in centipoise was calculated as described by Wells, Denton and Merril (1961).

In vitro *studies*

A plasma pool from four healthy males was obtained by the withdrawal of blood from a forearm vein into EDTA tubes.

One millilitre of any one of the cremophor anaesthetics was diluted 1 : 50 with 0.9% saline. After 1.8 ml of plasma was placed in the viscometer, shearing was started. When constant values were obtained at all five shear rates, 0.2 ml of the 1 : 50 diluted cremophor-containing anaesthetic was added to the sample cup making a final concentration of 1 : 500 in the plasma. This corresponds to an adult with 3 litre of plasma receiving 6 ml-cremophor-containing anaesthetic i.v. In fact, this was the dose required most frequently by the patients to keep them asleep.

Cremophor EL (BASF, Ludwigshaven) was dissolved in 0.9% saline to a concentration of 1 : 250. With 1.8 ml of plasma or dextran in the viscometer, a constant reading was obtained. Cremophor 1 : 250 0.2 ml was added, making a final concentration of 1 : 2500 of cremophor. This is the same dilution as obtained with 1 : 500 of the cremophor-containing anaesthetics, as these contain 20% cremophor.

Triton x-100 (Rhom & Haas) was dissolved in 0.9% saline to 1 : 250 and used in the same manner as was the cremophor.

Dextran 70 (Macrodex 6% with glucose, Pharmacia) was used undiluted in the viscometer. Urea (Analar) was obtained as dry substance in portions giving a concentration of 8 mol litre^{-1} when added directly to the sample cup with corrections for the expansion of volume.

The effect of urea 8 mol litre^{-1} on the viscosity of both plasma and 6% dextran was studied both before and after cremophor or Triton x-100 had been added.

RESULTS

In vitro *experiments*

In figure 1 the viscosity of the pooled plasma is plotted as a function of five different shear rates. The upper curve shows the normal viscosity pattern of plasma (open circles). The highest viscosity, 1.8 centipoise, was found at the lowest shear rate, 11.5 s^{-1}. After the addition of propanidid in a concentration of 1 : 500 the viscosity changed such that the smallest viscosity was at the slowest shear rate (fig. 1). The values found with the three different cremophor-containing anaesthetics differed, with a standard deviation of less than 5%. The change in the viscosity curve amounted to a 45% decrease at shear rate 11.5 s^{-1}. Dextran 70 had a constant Newtonian viscosity of 2.9 centipoise at all shear rates. It was decreased only 5–10% by cremophor-containing anaesthetics.

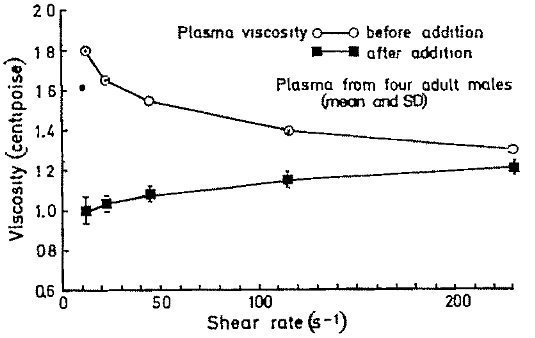

FIG. 1. *In vitro*: Epontol 1 : 500, cremophor 1 : 2500, Triton x-100 1 : 2500.

The addition of cremophor or Triton x-100 in a concentration of 1 : 2500 in plasma or dextran caused the same decrease in viscosity as did the cremophor-containing anaesthetics in a concentration of 1 : 500 (fig. 1).

The addition of urea 8 mol litre^{-1} to both normal and cremophor-containing plasma caused a steady increase in viscosity. After 30 min the plasma was converted to a clear jelly-like substance with a viscosity more than 100 times the starting value. Identical changes occurred when urea 8 mol litre^{-1} was added to the Triton-containing plasma. Dextran, on the other hand, showed only 25% increase in viscosity after urea 8 mol litre^{-1}.

In vivo *studies*

In 11 patients in whom anaesthesia was induced with diazepam with either propanidid or Althesin, the plasma viscosity was determined before and 5 min after induction. The total dose of cremophor-containing anaesthetic varied from 0.07 ml kg^{-1} to 0.15 ml kg^{-1}. A decrease in the plasma viscosity was found in all the patients, although there were marked variations from patient to patient. Figure 2 shows the mean and standard deviation for all the patients before induction of anaesthesia (open

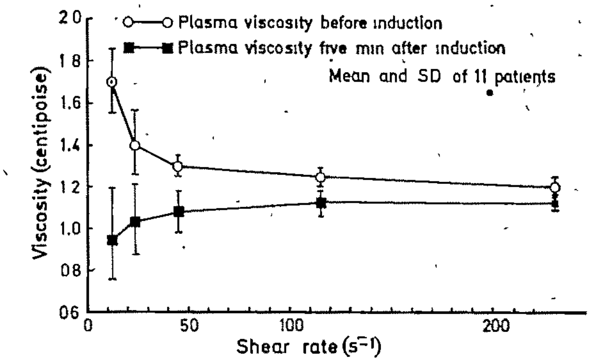

FIG. 2. Anaesthesia induction with cremophor EL anaesthetics.

circles) and 5 min after induction (closed squares). In three patients anaesthesia was induced with non-cremophor-containing anaesthetics to ascertain that it was not the induction of anaesthesia that caused the change in viscosity. In these patients diazepam 10 mg (Valium, Roche) and thiopentone 200 mg were used. In two of these patients there was a 10% increase in viscosity and in the other a 6% decrease.

In 18 patients plasma viscosity was determined before induction as well as 5, 10, 20, 30, 40 and 50 min after induction with cremophor-containing anaesthetics. A significant decrease of viscosity persisted in all the patients until 50 min after the injection. The decrease in viscosity at shear rate 11.5 s^{-1} expressed as a percentage of the value before induction has been plotted in figure 3 as a function of time. It is seen that this decrease in viscosity had disappeared by 50 min.

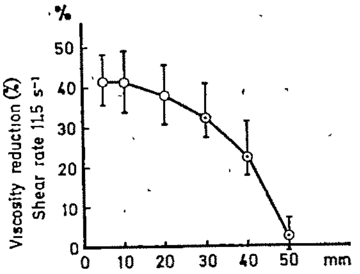

FIG. 3. Depression of viscosity after Cremophor EL anaesthetics. Rate of elimination of single dose (mean ± SD).

DISCUSSION

This study has demonstrated a 45% decrease in plasma viscosity *in vitro* after the addition of cremophor-containing anaesthetic agents or cremophor alone in a concentration corresponding to that obtained *in vivo*. A similar surfactant, Triton x-100, caused a similar decrease in viscosity. A decrease of 42% was found also *in vivo* 5 min after injection of an induction dose of the same anaesthetics. In both the *in vitro* and *in vivo* studies, it was noted that the cremophor anaesthetics depressed the viscosity mainly at the lower shear rates. The plot of plasma viscosity was thus changed from one of thixotropy to one of antithixotropy. The viscosity under normal circumstances is explained by an aggregation of protein molecules and formation of surface films. The change induced by cremophor must, therefore, be a result of elimination of these phenomena.

The effect of cremophor-containing anaesthetic agents is not a result of the sedative and sympatholytic effects of the induction of anaesthesia because thiopentone and droperidol cause smaller changes in viscosity (Aronsen, Magora and London, 1970; Magora et al., 1974). In our study only small changes in plasma viscosity were found in three patients in whom anaesthesia was induced with thiopentone and diazepam without cremophor.

In the patients whose results are given in figure 2, anaesthesia was induced with three different anaesthetics. It is most likely that the common solvent, cremophor, was responsible for the decreases in viscosity.

Cremophor is classified as a non-ionic surfactant (Blacow, 1972). Another non-ionic surfactant, Triton x-100, also a polyoxyethylated compound, has been found to reinforce the envelope of structured water surrounding protein molecules in solution. This was deduced from the fact that Triton x-100 increased the molecular volume and froze the active sites on the molecular surface (Koehler and Dowben, 1961). Triton x-100 disrupted paper–protein binding in electrophoresis, but had only a slight effect on polysaccharides. Concentrated urea 8 mol litre^{-1}, by its hydrogen bonding action, reversed these effects (Dowben, Koehler and Barrieux, 1961). This is analogous to our present finding that cremophor decreased the viscosity of plasma, but had very little effect on dextran. Urea 8 mol litre^{-1} increased the viscosity of both normal plasma and plasma containing cremophor or Triton x-100 more than 100 times. On dextran, however, it had only a minimal effect. The similarity in action between Triton x-100 and cremophor suggests a similar mechanism of action. An increased sheet of structured water disrupting aggregates of protein molecules may explain the action of cremophor.

The interaction of cremophor with plasma is obviously weak and reversible. This can be seen from figure 3, which shows that the high pre-induction viscosity of plasma returned after 50 min. This change is caused most probably by the disappearance of the cremophor from the blood. Infused triglycerides disappear from plasma in the same time interval (Schubert, 1976) and cremophor has been shown to comprise 84% triglycerides (Lorenz et al., 1977).

Cremophor causes histamine liberation in dogs (Wirth and Hoffmeister, 1965; Lorenz, Meyer et al., 1971). In the rabbit, pig and man, however, cremophor is not a histamine liberator and appears to be non-toxic (Doenicke and Lorenz, 1970; Lorenz, Barth et al., 1971; Lorenz, Meyer et al., 1971). No haemolytic or teratogenic effects in mice and rabbits have been shown. By adding small amounts of cremophor to ACD bank blood Reber (1965) showed that haemolysis was virtually abolished. As a solvent for diazepam, cremophor has proved superior to glycoferol–alcohol–benzoic acid with regard to occurrence of pain at the site of injection (Burton et al., 1974; Siebke, Ellertsen and Lind, 1976; Gjessing and Tomlin, 1977). It is possible that both plasma proteins and cell membranes are provided with a protective sheet of structured water in the presence of cremophor.

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AGENTS ANESTHESIQUES CONTENANT DU CREMOPHOR ET VISCOSITE DU PLASMA

RESUME

Des agents anesthésiques contenant du crémophor, tels que l'Althésine, le propanidid et le diazépam, ont été ajoutés à du plasma *in vitro*, puis administrés à des malades. *In vitro*, ces agents anesthésiques et le crémophor seul, en concentrations égales à celles obtenues *in vivo*, ont diminué la viscosité du plasma de 45% au taux de cisaillement de $11,5\ s^{-1}$. Sur 11 malades auxquels on avait administré des agents anesthésiants contenant du crémophor pour provoquer l'anesthésie, des échantillons de plasma obtenus 5 min après l'injection, ont fait ressortir une diminution moyenne de 42% dans la viscosité, par rapport aux valeurs relevées avant l'induction. L'effet sur la viscosité, après une seule dose, a disparu en 50 min. L'addition de Triton x-100 au plasma a provoqué une diminution de la viscosité, similaire à celle provoquée par le crémophor. On a trouvé que l'interaction *in vitro* du crémophor et du Triton x-100 avec de l'urée concentrée était identique aussi bien dans le plasma que dans le dextran. Ceci laisse penser que le crémophor agit en augmentant la couche d'eau structurée autour des molécules de protéine, empêchant de ce fait l'agrégation des protéines.

PLASMA-VISKOSITÄT UND CREMOPHOR-HÄLTIGE NARKOSEMITTEL

ZUSAMMENFASSUNG

Die cremophorhältigen Narkosemittel Althesin, Propanidid und Diazepam wurden *in vitro* Plasma beigemischt und an Patienten verabreicht. Diese Mittel sowie Cremophor allein in Konzentrationen wie sie *in vivo* erzeilt wer-

den, senkten die Plasmaviskosität um 45% in 11,5 s^{-1}. Bei 11 mit cremophorhaltigen Narkosemitteln behandelten Patienten zeigten die 5 min nach Injektion entnommenen Plasmaproben eine mittlere Verringerung der Viskosität von 42%, verglichen mit den vorherigen Werten. Die Wirkung auf die Viskosität durch eine einzelne Dosis verschwand nach 50 min. Dem Plasma beigefügtes Triton x-100 bewirkte eine Viskositätsverringerung ähnlich der durch Cremophor. Die Wechselwirkung *in vitro* von Cremophor und Triton x-100 mit konzentriertem Harnstoff war in Plasma und in Dextran identisch. Dies zeigt, dass die Wirkung von Cremophor durch eine Erhöhung der strukturierten Wasserhülle rund um die Proteinmoleküle erfolgt, wodurch die Zusammenballung der Proteine verhindert wird.

VISCOSIDAD DEL PLASMA Y ANESTETICOS QUE CONTIENEN CREMOFOR

SUMARIO

Los agentes anestéticos que contienen cremofor, Altesina, propanidido y diazepam, fueron añadidos al plasma *in vitro* y administrados a los pacientes. *In vitro* estos anestéticos y el cremofor solo en concentraciones iguales a las obtenidas *in vivo*, ocasionaron un descenso de la viscosidad del plasma de un 45% a un ritmo de deslizamiento de 11,5 s^{-1}. En 11 pacientes a los cuales se administraron anestéticos con cremofor para inducir la anestesia, las muestras de plasma recogidas 5 min después de la inyección revelaban un descenso medio de la viscosidad del 42% en comparación con los valores obtenidos en la pre-inducción. El efecto en la viscosidad después de una dosis única desapareció en 50 min. Al añadir Tritón x-100 al plasma, se obtuvo una disminución de la viscosidad similar a la conseguida con cremofor. La interacción *in vitro* del cremofor y del Tritón x-100 con urea concentrada se reveló idéntica tanto en el plasma como en el dextrán. Esto hace pensar que el cremofor provoca un aumento de la pared de agua estructurada alrededor de las moléculas proteínicas y, por lo tanto, impide el agregado de las proteínas.

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USE OF MANDATORY MINUTE VOLUME VENTILATION IN THE PERIOPERATIVE MANAGEMENT OF A PATIENT WITH MYASTHENIA

B. D. HIGGS AND J. C. BEVAN

SUMMARY

The anaesthetic and postoperative management of a patient with established myasthenia gravis, using a mandatory minute volume system (MMV), are described. Before operation the patient was receiving large doses of anticholinesterases and steroids. The anaesthetic and postoperative drug therapy and management were simplified by the use of the MMV system.

The anaesthetic management of patients with myasthenia gravis is complicated by their increased sensitivity to non-depolarizing myoneural blocking drugs and their resistance to depolarizing neuromuscular blocking drugs (Wylie and Churchill Davidson, 1972). Following operation the patient's ventilation must be monitored and may require assistance. It is a common practice to leave the endotracheal tube *in situ* for 24–48 h after the operation. Usually the patient's response to doses of anticholinesterase drugs is used as a guide to the progress of the myasthenia after surgery.

Mandatory minute ventilation (MMV), described by Hewlett, Platt and Terry (1977), is a system whereby a predetermined minute volume is delivered to the patient. The patient is allowed to breathe as much of this spontaneously as he can; the remainder of the minute volume fed to the system is delivered to him as intermittent positive pressure ventilation of the lungs. The pre-set minute volume may be exceeded by the patient, but the patient never receives less than the predetermined or mandatory minute volume. The system used in our patient was similar to that described by Hewlett, Platt and Terry (1977) using a Blease Brompton Manley ventilator. However, although the basic circuit design may be considered the same, the designs of the individual valves were different.

Three valves in line were sited on the inspiratory limb leading from the reservoir bellows:

(1) One-way valve enabling the spontaneously breathing patient to draw air from atmosphere. The preset minute volume may thus be exceeded by the patient.

(2) One-way valve preventing inflation of the reservoir bellows by the positive pressure ventilation delivered from the Brompton Manley ventilator.

(3) Safety blow off valve set at 70 cm H_2O to minimize trauma to the patient from excessively great airway pressures. The valves listed above were manufactured and supplied by Penlon Ltd.

Two valves were sited on the common expiratory limb leading from the ventilator:

(1) One-way valve positioned to prevent the patient drawing air from atmosphere through the expiratory limb of the system.

(2) A positive end-expiratory pressure valve. This was removed when not in use. Both the above were manufactured and supplied by Siemens Elema.

Wright's respirometers were positioned on the inspiratory limb leading from the reservoir bellows and the inspiratory limb leading from the ventilator. These recorded inspired tidal and minute volumes from spontaneous and automatic ventilation.

A third respirometer in the common expiratory limb measured expired tidal and minute volumes.

The cut-off valve leading to the reservoir bellows was similar in design to that described by Pfitzner (1976).

CASE REPORT

An 81-yr-old female underwent abdomino-perineal resection for Crohn's disease of the large bowel in 1973. Anaesthesia was uneventful and depolarizing and non-depolarizing neuromuscular blocking drugs were used. Shortly before this admission the patient had complained of ptosis, but neurological assessment

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revealed no other abnormality and an edrophonium test was negative.

Myasthenia gravis was diagnosed in August 1977 when the patient was admitted with a bulbar weakness which improved with edrophonium. The longstanding ptosis was unresponsive. Chest x-ray showed the presence of a large thymoma (fig. 1), but it was not considered to be in the patient's best interest to attempt its removal. Anticholinesterase therapy was commenced.

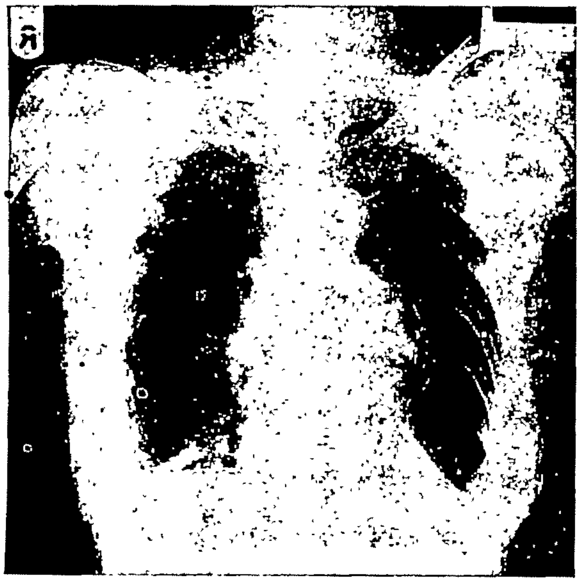

FIG. 1. Chest x-ray showing presence of large thymoma.

In September 1977 the patient had a relapse and required tracheal intubation and intermittent positive pressure ventilation of the lungs for 9 days. Steroid therapy was commenced. She was well enough later to permit discontinuation of the automatic ventilation while continuing to take, orally, pyridostigmine 30 mg 3-hourly and prednisone 50 mg and 25 mg alternate days.

On April 12, 1978 the patient underwent a further resection of the bowel and resiting of the colostomy. Premedication consisted of hydrocortisone 100 mg and pyridostigmine 1 mg i.m. Anaesthesia was induced with thiopentone 100 mg i.v. and maintained with halothane 1.0–1.5% in 60% nitrous oxide in oxygen with a mask. Nasotracheal intubation was accomplished easily after 5 min. The patient continued to breathe spontaneously the mixture of nitrous oxide, oxygen and halothane through an MMV system. The appropriate minute volume for the patient was derived using a Radford nomogram (Radford, 1955) and this was fed to the system described earlier.

An extra 1 litre of the anaesthetic gas was then introduced into the system. The patient's minute volume was thus exceeded, and a slow smooth transition from spontaneous breathing to controlled artificial ventilation took place over a period of about 5 min. Surgery was performed with good operating conditions. The patient received controlled ventilation throughout the whole procedure. The electrocardiogram, arterial pressure and heart rate were monitored continuously and were unremarkable.

At the end of the operation the minute volume fed to the system was reduced by 1 litre. Halothane and nitrous oxide were discontinued and the patient received oxygen 100%. Over a period of about 5 min there was a smooth transition from controlled to spontaneous ventilation.

The patient was transferred to the intensive care unit. The tracheal tube was left *in situ* and remained connected to the MMV system. A radial artery cannula was inserted to facilitate monitoring of blood-gas tensions. The initial blood-gas analysis confirmed that the minute volume given to the patient was adequate. Thereafter the patient breathed a mixture of air and oxygen with the inspired oxygen concentration adjusted to maintain Pa_{O_2} at an acceptable value.

Steroid therapy was continued and pethidine 25 mg was given for pain. Expired minute volume and tidal volume were measured continuously and blood-gases were analysed every 2 h. E.c.g., arterial pressure, heart rate and respiratory rate were monitored also. Routine care of the tracheal tube and the patient was carried out by the nursing staff. In view of the patient's high requirements for pyridostigmine before operation, at 23.00 h she was given pyridostigmine 0.5 mg i.m. to avoid any possible deterioration in neuromuscular power that might embarrass respiration or decrease her ability to cough overnight. The blood-gas state remained stable (table I) and there was no alteration in measured minute volume expired or tidal volume overnight.

For approximately 24 h after operation the patient continued to breathe spontaneously, maintaining satisfactory blood-gas values. The tracheal tube was removed but the patient remained in the intensive care ward for a total of 5 days. During this time there was no apparent deterioration in muscle power. Diagnostic edrophonium tests were performed daily, and sometimes twice daily, and no therapeutic anticholinesterases were found necessary. Tidal volume,

TABLE I. *Results of blood-gas analysis.* * *Following pethidine*; † *following pyridostigmine*; ‡ *extubated*

	Day 1—hours after operation							
	0	2	4*	8	12†	Day 2‡	Day 2	Day 2
Minute volume (litre min^{-1})	6	6	6	6.7	7.0	7.0	6.5	6.5
Inspired oxygen concn (%)	30	30	30	30	30	21	21	21
Pa_{O_2} (kPa)	12.7	15.9	14.9	14.6	15.2	10.1	9.3	8.9
Pa_{CO_2} (kPa)	5.5	5.5	5.5	5.1	4.6	4.6	5.0	4.9
pH (units)	7.36	7.34	7.36	7.34	7.41	7.44	7.42	7.42
Non-respiratory pH	7.39	7.37	7.38	7.33	7.37	7.39	7.40	7.40

minute volume and peak flow measurements were made 2-hourly for 2 days and thereafter twice daily in the intensive care ward, and were always within normal limits. Blood-gas analysis was continued 2-hourly for 24 h and then the radial artery line was removed. A radial artery sample obtained by direct puncture was analysed once a day for the remainder of the patient's stay in the intensive care ward.

On returning to the general ward the patient was receiving only steroid therapy on a regular basis. Clinical assessment and peak flow measurements were performed regularly in the ward and it was not considered necessary to restart her anticholinesterase regime. The patient still receives prednisone 12 mg daily, and this is now being reduced.

DISCUSSION

The anaesthetic management of patients with myasthenia gravis for unrelated surgical conditions can prove difficult. The major problems are the maintenance of adequate ventilation with the provision of adequate relaxation, and the clearance of secretions.

A large thoracic or abdominal incision makes it imperative that the trachea is intubated and the lungs are ventilated. Halothane provides satisfactory anaesthesia and some degree of muscular relaxation, obviating the need for neuromuscular blocking drugs.

In the period after operation there are two main problems, the restoration of adequate neuromuscular transmission and the maintenance of adequate ventilation. The hazards following operation are well described (Mushin, 1971) and it is agreed that patients should be supervised closely in an intensive care unit as long as they are at risk (Bryan-Brown, 1971).

The use of MMV in our patient simplified the management and allowed trouble-free weaning from intermittent positive pressure ventilation. Anaesthesia was induced, controlled ventilation of the lungs ensured, and relaxation produced in a safe, simple and effective way. There was no requirement for any neuromuscular blocking agents, peripheral nerve stimulation or anticholinesterase drugs at any time.

In the period after operation, if respiratory muscle power deteriorates for any reason the MMV system will maintain the patient's minute volume. The observation of the change from entirely spontaneous ventilation to part spontaneous ventilation–part intermittent positive pressure ventilation of the lungs, or to complete intermittent positive pressure ventilation of the lungs may be used as an indication that anticholinesterase drugs are required. Sufficient anticholinesterase drugs will restore spontaneous ventilation. Should a relative overdose of anticholinesterase drugs be given, causing a cholinergic crisis, the patient's minute volume will be maintained. This management can be continued until adequate spontaneous breathing is maintained and a suitable anticholinesterase regime is determined. The patient described was safely transferred to the intensive care unit where she was permitted to breathe spontaneously. She maintained adequate spontaneous ventilation throughout the postoperative period and required no anticholinesterase drugs during this period, despite requiring large doses before operation.

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USAGE DE LA VENTILATION OBLIGATOIRE BASEE SUR LE DEBIT CARDIAQUE POUR LE TRAITEMENT PERIOPERATOIRE D'UN MALADE SOUFFRANT DE MYASTHENIE

RESUME

On décrit dans cet article l'anesthésie et le traitement postopératoire à l'aide d'un système obligatoire basé sur le débit cardiaque (MMV), d'un malade souffrant d'une myasthénie grave bien déterminée. Avant l'opération, le malade recevait de fortes doses d'anticholinestérases et de stéroïdes. L'anesthésie et la chimiothérapie postopératoire ainsi que les soins d'ensemble ont été simplifiés grâce à l'usage du système MMV.

VERWENDUNG EINES OBLIGATORISCHEN MINUTENVOLUMEN–BELÜFTUNGSSYSTEMS BEI POSTOPERATIVER BEHANDLUNG EINES PATIENTEN MIT MYASTHENIA GRAVIS

ZUSAMMENFASSUNG

Die anästhetische und postoperative Behandlung eines Patienten mit etablerter Myasthenia gravis durch ein obligatorisches Minutenvolumen–Belüftungssytem (MMV) wird beschrieben. Vor der Operation erhielt der Patient grosse Dosen von Anticholinesterase und Steroiden. Die anästhetische und postoperative Drogentherapie und Behandlung wurden durch Verwendung des MMV-Systems vereinfacht.

USO DE VENTILACION DE VOLUMEN-MINUTO OBLIGATORIO EN LA GESTION PERI-OPERATORIA DE UN PACIENTE CON MIASTENIA GRAVIS

SUMARIO

Se hace una reseña de la gestión post-operatoria y anestética de un paciente con miastenia gravis establecida mediante el sistema de volumen-minuto obligatorio (VMO). Antes de la operación, el paciente recibía grandes dosis de anticolinesterasas y de esteroides. Se simplificaron la terapia y la gestión químicas postoperatorias y anestéticas mediante el sistema VMO.

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THE JOHANNESBURG A–D CIRCUIT SWITCH

A valve device for converting a co-axial Mapleson D into a co-axial Mapleson A system

A. W. MANICOM AND C. G. SCHOONBEE

SUMMARY

A simple valve device is described for a co-axial tubing anaesthetic system which enables selection of the circuit characteristics of either a modified Mapleson A system for spontaneous breathing or a modified Mapleson D system for controlled ventilation. Thus, the system allows an economical fresh gas flow to be used during either controlled or spontaneous ventilation. The mode of ventilation may be changed during anaesthesia without adjusting the patient tubing or the attachment of the system to the anaesthetic machine.

The characteristics of the Mapleson D anaesthetic system enable economy of fresh gas flow during controlled ventilation. However, during spontaneous ventilation a high fresh gas flow is required to prevent rebreathing of alveolar gas. The Mapleson A system, in contrast, is economical only during spontaneous ventilation.

An anaesthetic system using co-axial tubing has been described by Ungerer and le Roux (1978) which enables a modified Mapleson D or a modified Mapleson A system to be selected by interchanging the positions of the fresh gas inlet and the relief valve. We describe a switching valve known as the "Johannesburg A–D circuit switch" which simplifies the selection of either the Mapleson A or Mapleson D characteristics of the system referred to above.

DESCRIPTION

A prototype valve and co-axial circuit are shown in figure 1. The outer tube consists of light-weight corrugated p.v.c. tubing of 25 mm internal diameter (i.d.). The inner tube is smooth-walled and has an i.d. of 12.5 mm and an outside diameter (o.d.) of 15 mm. Both tubes are 1.5 m long. Disposable tubing was used in the prototype.

The separate components of the switching valve are shown in figure 2. A mobile switch disc (5) contains two 12.5-mm, bean-shaped channels. When rotated to position "A" the switch disc connects the fresh gas inlet port (1) to the lumen of the outer tube via port 2. In this position port 3 is connected to port 4, which allows excess gas to be vented from the inner tube through the relief valve, thereby producing the characteristics of a co-axial Mapleson A system. By rotating the switch disc through 90° to position "D", the order is reversed so that fresh gas is directed to the inner tube via ports 1 and 3 and excess gas reaches the relief valve from the outer tube via ports 2 and 4. The system thus has the characteristics of a co-axial Mapleson D system.

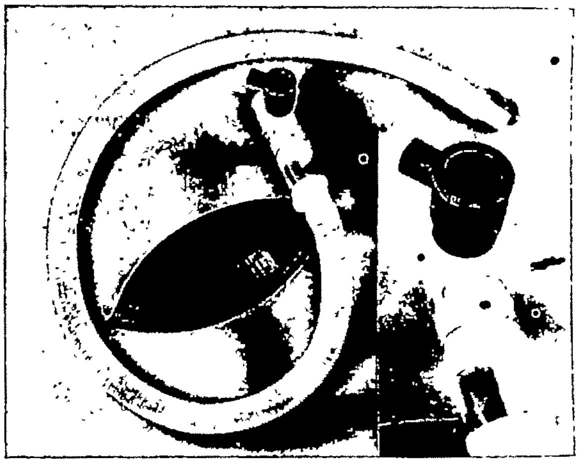

FIG. 1. The circuit with switching valve in position. Enlargement of switching valve, inset.

DISCUSSION

The behaviour of the co-axial Mapleson D anaesthetic system (Bain system) during controlled ventilation with low fresh gas flows has been studied extensively (Bain and Spoerel, 1973; Spoerel and Bain, 1975;

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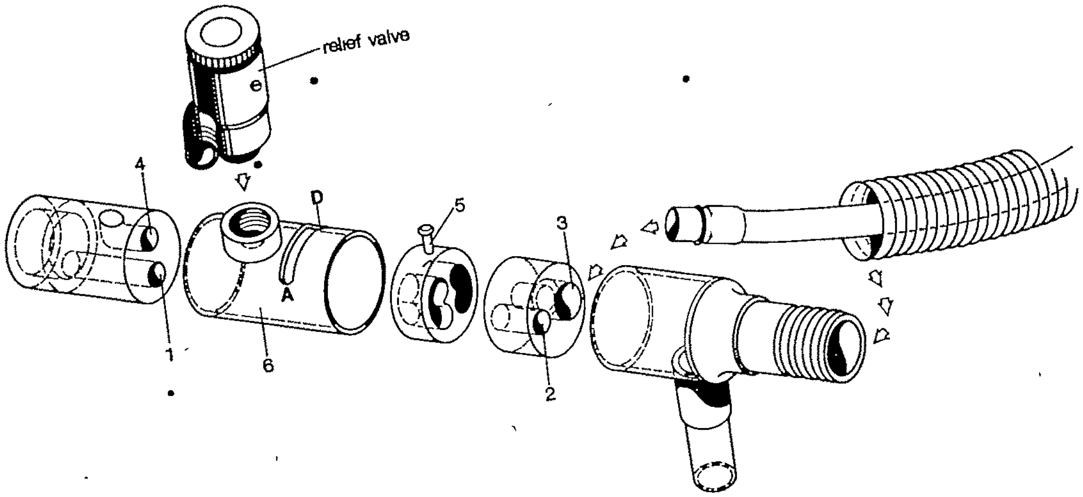

FIG. 2. Exploded isometric view of the valve. 1 = Fresh gas inlet port. A standard 22-mm taper fixes the system to the anaesthetic machine gas outlet. 2 = Port through which fresh gas passes to outer tube with switch in position "A". Excess gas exits through same port when switch is in position "D". 3 = 15-mm taper port through which fresh gas passes to inner tube with switch in position "D". Excess gas is vented from the inner tube and this port when switch is in position "A". 4 = 12.5-mm diameter channel leading to relief valve. 5 = Mobile switch disc with lever and containing two 12.5-mm bean-shaped channels. 6 = Transparent plastic sleeve with relief valve mount which holds components in place. A slot limits movement of the lever-operated switch disc.

Henville and Adams, 1976). The system may be used for patients of all ages where controlled ventilation is required, and is especially useful when access to the patient is limited. The tubing produces minimal drag on the tracheal tube and the system facilitates scavenging of waste gas. Controlled ventilation using a fresh gas flow of 70 ml kg^{-1} and a minute volume of 140–160 ml kg^{-1} allows normocarbia to be maintained. During spontaneous ventilation, however, a high fresh gas flow of three times the minute volume is required to prevent rebreathing (Conway, Seeley and Barnes, 1977).

The Mapleson A (Magill) system is ideal for spontaneous ventilation requiring fresh gas flows of 70–80 ml kg^{-1} (Kain and Nunn, 1968; Norman, Adams and Sykes, 1968). A co-axial Mapleson A system was designed by Lack (1976) in order to facilitate scavenging of waste anaesthetic gas. An early prototype of this system proved to have high resistance to breathing and required a relatively great fresh gas flow during spontaneous ventilation (Barnes et al., 1976).

Subsequently, Ungerer and le Roux (1978) have shown that, by using wide-bore co-axial tubing consisting of an outer tube of 27 mm i.d. and an inner tube of 12.5 mm i.d., the co-axial Mapleson A system would behave in a manner similar to the Magill system, requiring a similar fresh gas flow during spontaneous ventilation and having an acceptable resistance to breathing. It was shown that by interchanging the positions of the fresh gas inlet and the relief valve, the system could be converted to a co-axial Mapleson D system.

The Johannesburg switching valve provides additional advantages for such a co-axial system: a change from the Mapleson A system to the Mapleson D system is effected simply by movement of the switch disc lever; the attachment of the apparatus to the anaesthetic machine need not be altered; the position of the relief valve remains constant, enabling scavenging to be continuous; clear markings guard against the possibility of selecting the wrong system in clinical use.

The switching valve has wide-bore channels which minimize resistance to gas flow. Using a water manometer and a 30 litre min^{-1} flow of air from a calibrated rotameter, the pressure decrease across the length of the inner tube and switching valve fitted with a Medishield shrouded relief valve was 254 Pa (2.6 cm H_2O) which represents the expiratory resistance of the co-axial Mapleson A system. The inspiratory resistance of the co-axial Mapleson A system was 49 Pa (0.5 cm H_2O) at 30 litre min^{-1} flow.

As a dangerous situation may develop if the inner tube of a co-axial system becomes disconnected, a firm 15-mm taper joint is used for the junction of the inner tube and switching device. The joint is always visible through the clear plastic outer housing.

The components may be cleaned and sterilized without dismantling. However, should separation be necessary, they are keyed to prevent incorrect reassembly.

ACKNOWLEDGEMENTS

We are grateful to Professor C. H. van Hasselt, Head of Department of Anaesthesia, University of Witwatersrand, for his encouragement with this project. Illustrations were supplied by the Medical Illustration Department, University of Witwatersrand.

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L'INTERRUPTEUR DE CIRCUIT A–D DE JOHANNESBOURG

Dispositif à soupape pour convertir un système coaxial Mapleson D en un système coaxial Mapleson A

RESUME

On décrit dans cet article un dispositif simple comportant une soupape, destiné à un système anesthésique à tubage coaxial qui permet de sélectionner les caractéristiques du circuit, soit d'un système Mapleson A modifié pour la respiration spontanée, soit d'un système Mapleson D modifié pour la respiration contrôlée. Ainsi ce système permet d'utiliser un débit économique de gaz frais, pendant la ventilation contrôlée ou pendant la ventilation spontanée. Le mode de ventilation peut être modifié pendant l'anesthésie sans ajustement du tubage du patient ou sans toucher au système de fixation à la machine d'anesthésie.

DER JOHANNESBURG-A–D-SCHALTER

Eine Ventilvorrichtung zur Umwandlung eines koaxialen Mapleson D-Systems in ein koaxiales Mapleson A-System

ZUSAMMENFASSUNG

Beschrieben wird eine einfache Ventilvorrichtung für ein koaxiales Anästhesie-Rohrleitungssystem, das die Auswahl von Schaltkreiseigenschaften entweder eines modifizierten Mapleson A-Systems für spontanes Atmen oder eines modifizierten Mapleson D-Systems fur kontrollierte Beatmung gestattet. Das System gestattet daher die Verwendung eines wirtschaftlichen Frischgasstromes sowohl bei spontaner wie bei kontrollierter Beatmung. Die Beluftungsmethode kann während der Narkose geändert werden, ohne dass die an den Patienten angeschlossenen Rohrleitungen oder der Anschluss an den Narkoseapparat verändert werden müssen.

INTERRUPTOR DEL CIRCUITO A–D DE JOHANNESBURGO

Un mecanismo de válvula para convertir un sistema coaxial Mapleson D en un sistema coaxial Mapleson A

SUMARIO

Se describe un simple mecanismo de válvula para sistema de anestesia por tubería coaxial que permita la selección de características del circuito: ya sea un sistema Mapleson A modificado para respiración espontánea ya sea un sistema Mapleson D modificado para ventilación controlada. Por ende, el sistema permite un flujo económico de gas fresco a usarse en ventilación espontánea o controlada. Puede modificarse el modo de ventilación en el curso de la anestesia sin ajustar la tubería del paciente ni la conexión del sistema a la máquina anestesiadora.

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CORRESPONDENCE

CHAGAS' DISEASE

Sir,—In its chronic phase, Chagas' disease is associated with destruction of autonomic nervous system components, principally parasympathetic innervation (Koeberle, 1958, 1959, 1963, 1970; Alcantra, 1971; Oliveira, 1969; Santos, Ramos de Oliveira and Koeberle, 1976).

Chagasic cardiomyopathy with total A–V block is found in patients aged 20–50 yr. This contrasts with other cardiomyopathies in which A–V block occurs in the later decades of life. These patients react differently when undergoing treatment for total A–V block. Finck, Frank and Zoll (1969) have recommended the use of nitrous oxide in oxygen after the use of suxamethonium for tracheal intubation, isoprenaline as a chronotropic agent and digitalis and procainamide for the control of atrial and ventricular arhythmias. We consider that this technique is not suitable for patients with decompensated Chagas cardiomyopathy. Digitalis and procainamide are contraindicated because of their negative chronotropic and inotropic properties. Isoprenaline, a sympathomimetic drug, would aggravate the predominance of chronic sympathetic tone already present in Chagas' disease and which is more marked in the decompensatory phase. We no longer use atropine sulphate before operation because it may provoke ventricular irritability (Payne, 1971). Beta-adrenergic blockade might jeopardize haemodynamic function. Bretyllium tosylate has a selective sympathetic blocking action with no effect on myocardial contractility and would appear to be the drug of choice (Maranhao et al., 1971).

From December 1970 to June 1977, 218 patients with Chagas cardiomyopathy and Stokes–Adams syndrome with total atrio-ventricular block were anaesthetized for surgical implantation of an epicardial pacemaker. Thirty-three of these presented in a state of cardiac decompensation with a marked decrease in cardiac output, cardiac arhythmia, metabolic acidosis and with clinical symptoms of sweating, coldness and cyanosis of the extremities. pH, Pa_{CO_2} and base excess were measured; the metabolic acidosis was corrected with sodium bicarbonate 8.4%. Droperidol 2.5–5 mg was administered i.v. to provide sedation in the distressed patient.

We have modified our anaesthetic technique since we presented our first 30 cases in a preliminary report at the IV World Congress of Anaesthesiology (Barreto, Kaadi and Souza, 1972). Recently, we have used diazepam 0.2 mg kg^{-1} for hypnosis, fentanyl 0.01 mg kg^{-1} as analgesic and pancuronium bromide 0.1 mg kg^{-1} as muscle relaxant; anaesthesia was maintained using 50% nitrous oxide in oxygen. Morphine or fentanyl used either alone (Lowenstein et al., 1969) or with neuroleptic drugs (Oliveira, Melo and Monteiro, 1969) would be the best anaesthetic technique for a high-risk cardiac patient. Improvement as a result of more efficient myocardial oxygenation would be expected after the pacemaker insertion. However, extrasystoles from electrode tip irritability are common after it is installed and we used lignocaine as an anti-arhythmic drug (Cullhed, 1960).

All patients were nursed in the I.T.U. and mechanical ventilation of the lungs was maintained until the neuromuscular blocker and analgesic drugs were metabolized and consciousness had returned.

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SKIN PENETRATION OF KETOCAINE

Sir,—In the discussion of the paper "The Teaching of Obstetric Extradural Analgesia" (Åkerman, 1979) Dr Åkerman used a radio-tracer method to demonstrate the relative penetration into skin of ketocaine and an inert vehicle, isopropanol. However, the ketocaine was labelled with hydrogen-3 and the isopropanol with carbon-14 and this gives rise to a query as to whether some part of the greater penetration recorded for ketocaine resulted from the lability of hydrogen-3 atoms alone. It was demonstrated some time ago that tritium can exchange readily with hydrogen atoms in tissue (Siri and Evers, 1961) hence the reported penetration into skin of the hydrogen-3 label may not necessarily correspond exactly to the penetration of ketocaine. Since ketocaine can also be labelled with carbon-14 it would be interesting to compare the results using this radio-tracer in both anaesthetic and inert vehicles.

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Sir,—The work of Siri and Evers to which Mr Smythe refers is concerned with the exchange that can occur between tritium and labile hydrogen atoms when tritium-labelled water is used as a solvent or tracer in biological systems. Under the experimental conditions that we have used it is probable that the radioactivity represents the ^{3}H-ketocaine that has penetrated the skin. We share Mr Smythe's opinion that ^{14}C-labelling is preferable in certain situations, but we consider that the use of tritium-labelling in our experiments has been adequate even with regard to the pitfalls that may be associated with studies involving tritium-labelled compounds.

B. Åkermann
Sweden

9th OBSTETRIC ANESTHESIA CONFERENCE

The Ninth Obstetric Anesthesia Conference will be held at the Sheraton Waikiki Hotel, Oahu, Hawaii, on March 30–April 5, 1980. This meeting is sponsored by the Department of Anesthesiology at Ohio State University.

A complete programme or further information can be obtained from:

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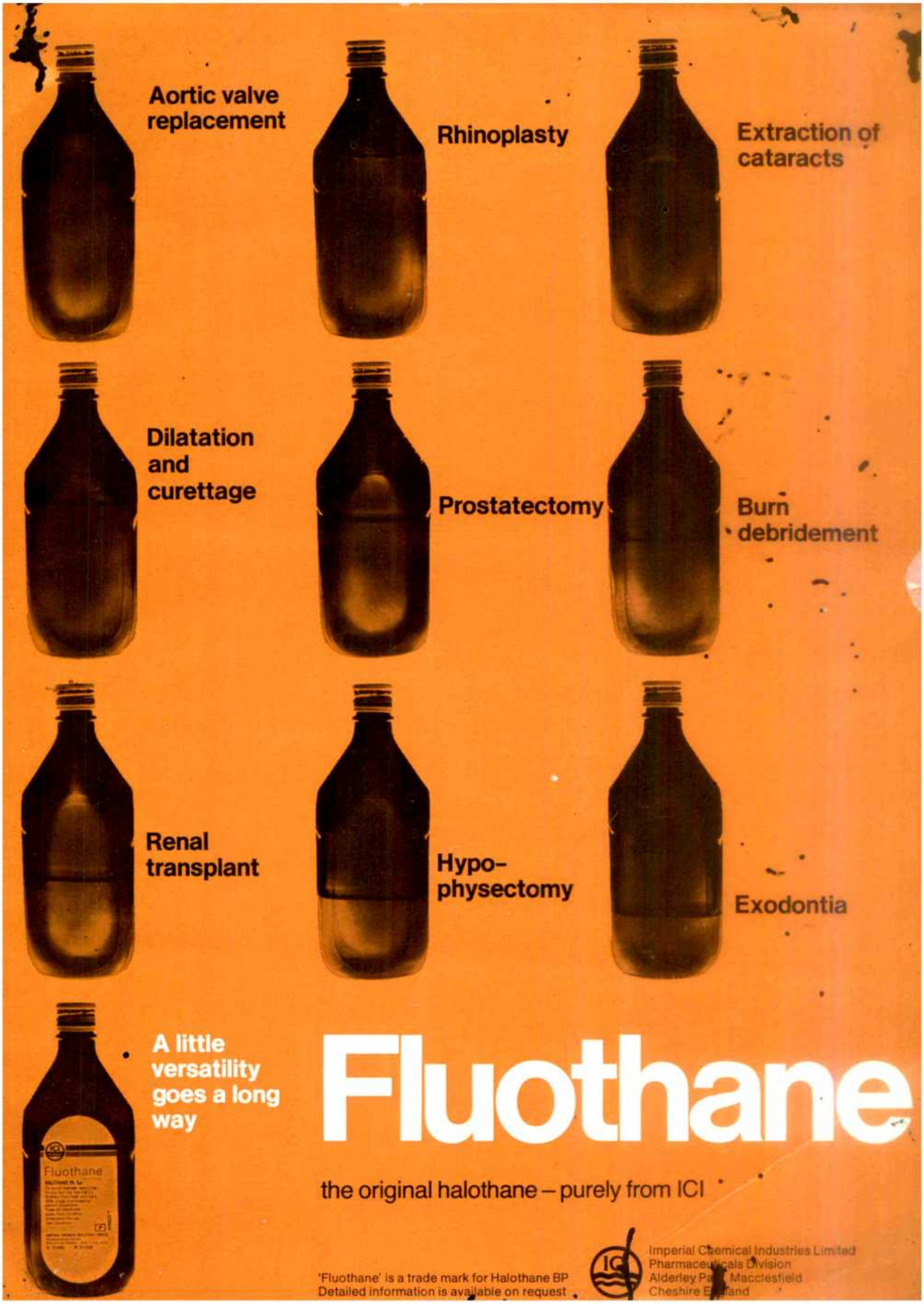

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